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Experience gained through over 100 years of artificial eyemaking enables us to produce and fit the very finest in eyes of glass and plastic.

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Integration of the Troutman magnetic implant is accomplished without the use of a pin attachment for direct transmission of motility, but through the use of a magnetic field which is created between the implant and the prosthesis by the use of magnets in both. This allows *complete coverage* of the implant by *Tenon's and the conjunctiva* and still maintains positive integration.

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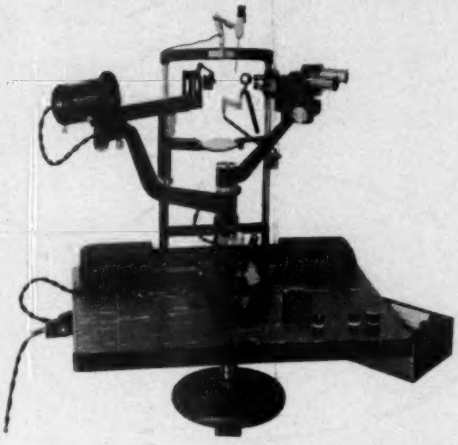
DOCTOR—

this new Haag-Streit slit lamp

HAS MANY OUTSTANDING ADVANTAGES

YOU SHOULD INVESTIGATE



A single control handle (joystick type) permits instant adjustment, either gross or minute, in any direction.

The elevation control is located near the "joystick" so that all adjustments are made with one hand, leaving the other hand free for working on patient's eye.

When the miscroscope is perfectly focused, the slit beam is also perfectly focused in the center of the field of observation.

The optical section remains adjusted when changing plane or area of examination.

Four magnifications available (up to 40X).

Brilliant illumination with very convenient slit adjustment.

Using accessories, it is possible to examine the fundus and get a true optical section and to do Slit lamp gonioscopy with patient seated at a normal Slit lamp installation.

Standard Accessories:

Goldmann Reduction Prism • Illuminated Fixation Device
Hruby-55 Diopter Lens for fundus examination
Contact glass for fundus examination
Contact glass for gonioscopy
Measuring Eye Piece and Ulbrich Drum to measure depth and plane in the eye.

Extra Accessories:

Tyndallimeter—to measure corneal haze
Second Observer's Eye Piece complete with inside pointer for teaching and clinical use.

The House of Vision Inc.

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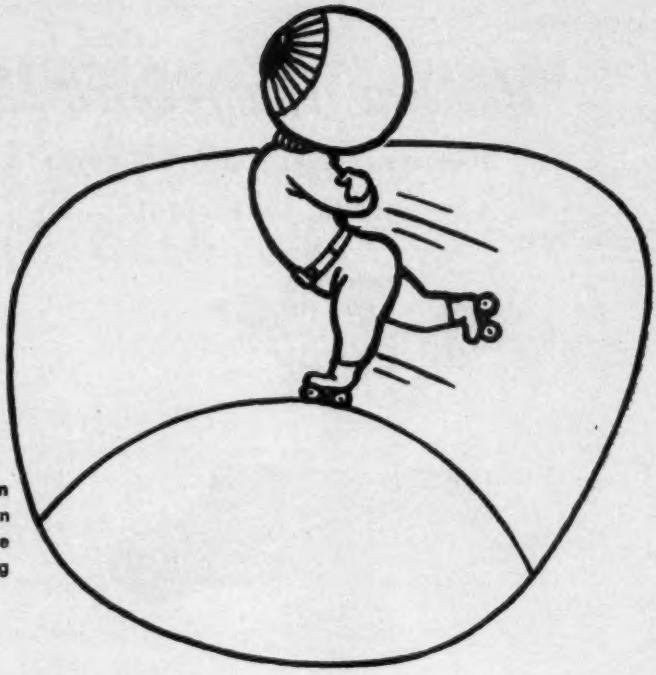

Segment Size: 32 x 38 m/m
AL is something special you can offer. Weight and excessive color prohibit this style being made except in Onepiece.

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ONEPIECE BIFOCAL

As an easy transition lens for new emmetropic presbyopes.

Give patients unused to glasses freedom

from that "boxed in" feeling through AL's

high, wide, less restricted reading field.

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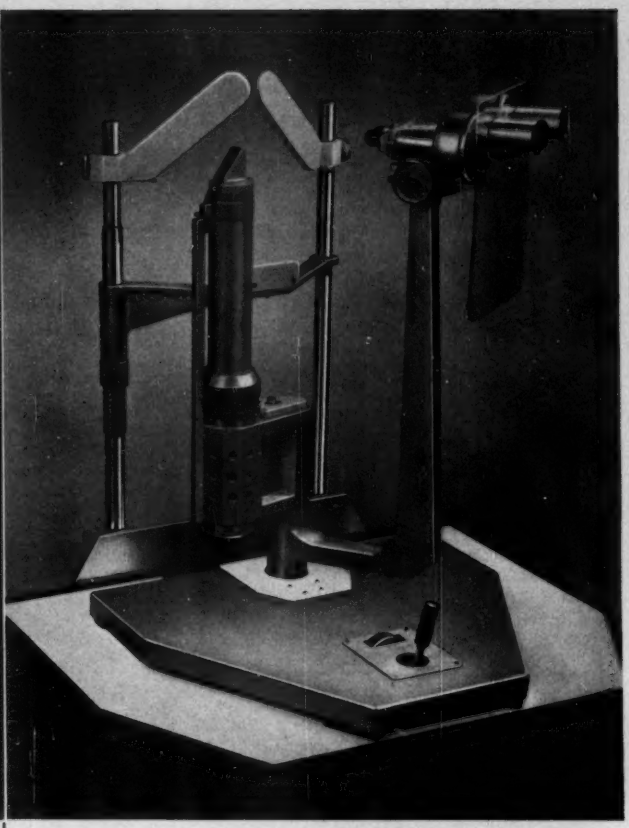

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For Microscopy of the Anterior Segment of the Eye and Fundus

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Apparatus supplied complete with table. Hruby lens attachment available. Prices on application.

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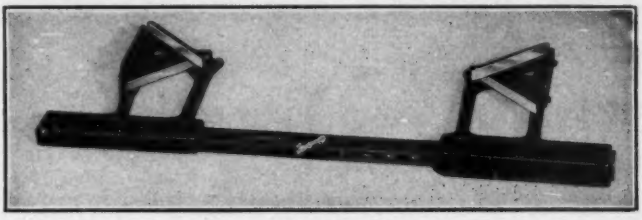
HERTEL EXOPHTHALMOMETER

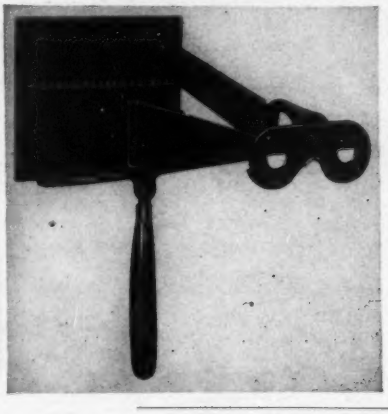


Improved over the original German model, in that it has front surface mirrors which do away with parallax, this exophthalmometer enables the examiner to measure the degree of exophthalmia accurately and rapidly without assistance.

The right member slides over a calibrated millimeter rule. Each member has two mirrors mounted at right angles, one above the other. When the instrument is in position, with the two outer points in contact with the temporal margin of each orbit, the profile of the cornea is seen in one mirror and the scale in the other. The scale reading directly above the corneal image gives its protrusion in millimeters.

The separation of the two members is shown on the slide. All measurements of the same case must be made with the members separated to the same reading on the sliding scale. Supplied in case. **Price $55.00**

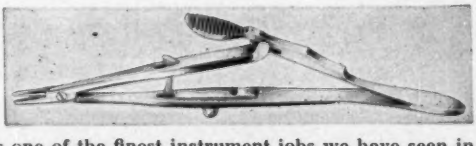
MADDOX WING TEST



Horizontal and vertical deviations and cyclophoria may be measured on the chart of this instrument. The red arrow points to a vertical row of red figures and indicates the degree of hyperphoria. The white arrow points to a row of horizontal figures and indicates es- or exophoria. Cyclophoria is denoted when the red arrow does not appear parallel to the horizontal white line and its degree is recorded on the small scale at the right of the chart. The working distance is 33 cms. and the horizontal and vertical deviations are recorded in prism diopters.

Price $24.50

KALT NEEDLE HOLDER



Even though not imported, this is one of the finest instrument jobs we have seen in recent years. The jaws are small and evenly serrated; the tension just right—grips just before it locks. The lock is silent and releases at a touch. In stainless steel. **Price $24.00**

THE BAUSCH & LOMB PANOPTIK BIFOCAL IS THE

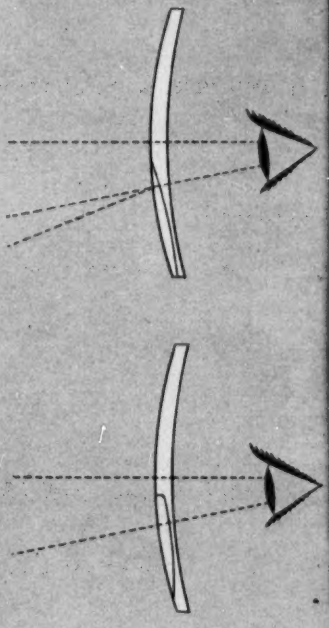
NATURAL VISION LENS

...patients see things *where they are...*

The Panoptik construction principle provides for complete flexibility in exact placing of the optical center of the segment. It has been placed near the top of the segment to eliminate the apparent displacement of objects as vision passes from distance portion to segment. Floors do not "slope up," steps do not "jump up." The Panoptik wearer has *natural vision*, safe and comfortable as with single vision lenses.

in Soft-Lite, too

A new Bausch & Lomb booklet, "Natural Vision," tells what patients want in a bifocal lens, describes the characteristics which result in Panoptik's superior performance among bifocals, trifocals and special purpose multifocals. Ask your Bausch & Lomb distributor's representative.



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The Purpose of the Guild

- The aim of the Guild of Prescription Opticians of America is to advance the science of ophthalmic optics through the development of a country-wide ethical optical dispensing service that comprehensively meets the needs of the Eye Physicians and their patients; and to educate the public to the fact that the Eye Physician-Guild Optician type of eye service truly renders the most desirable form of eye care.

This statement of the Guild's purpose is reprinted from the cover of the REFERENCE LIST OF GUILD OPTICIANS, a geographical index of all our members. If you would like a copy, just drop a penny post card to

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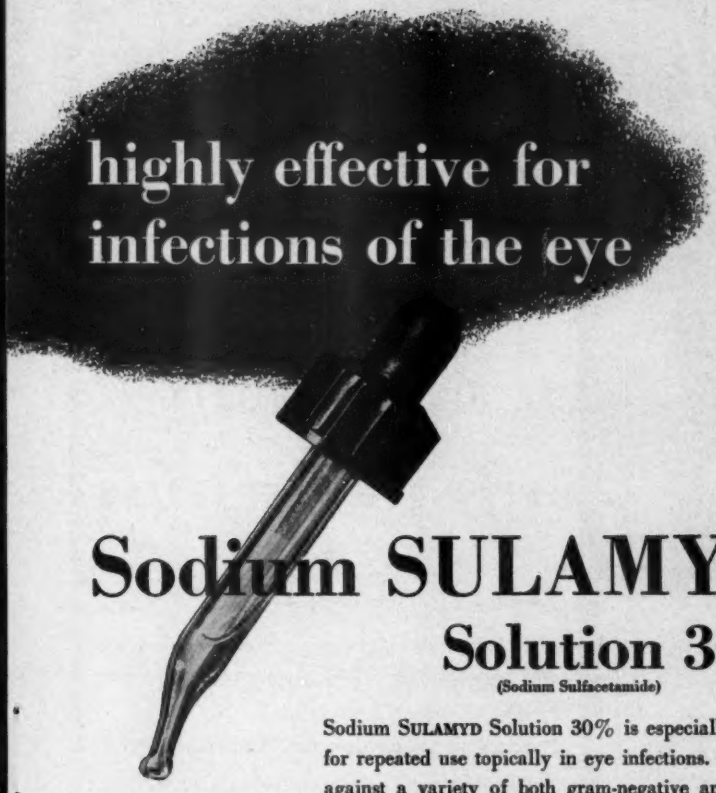
highly effective for infections of the eye



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(Sodium Sulfacetamide)

Sodium SULAMYD Solution 30% is especially suited for repeated use topically in eye infections. Effective against a variety of both gram-negative and gram-positive organisms, it cures most acute eye infections with little risk of sensitization.

For treatment, instill one drop every two hours or less frequently according to severity. Following removal of a foreign body, instill one drop four to six times daily for two days.

Sodium SULAMYD Solution 30% (Sodium Sulfacetamide) is available in 15 cc. eye-dropper bottles. A 10 per cent ophthalmic ointment is available for application to lids and conjunctiva.

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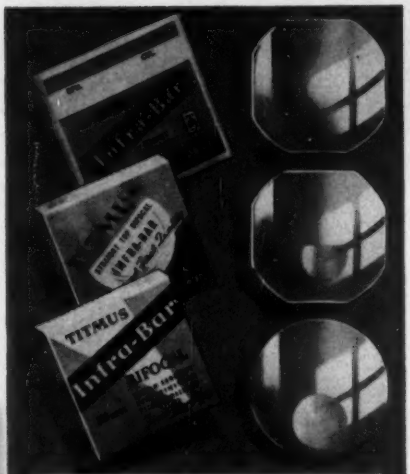
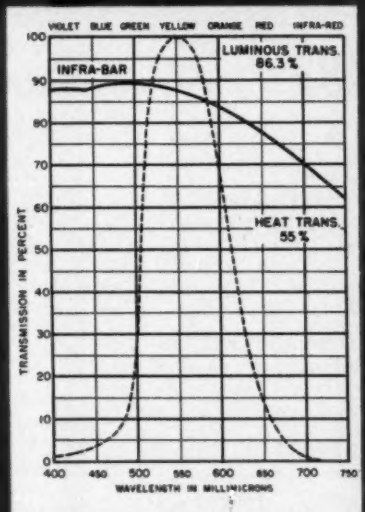
Sodium SULAMYD Solution 30%

TITMUS *takes pride in announcing the new*





● The broken line indicates visual sensitivity of the eye. The solid line is the Infra-Bar transmission curve.

At 2 mm. thickness, the luminous transmission of Infra-Bar for I.C.I. Illuminant C (daylight) is 86.3%. This may be compared with 92% luminous transmission of white crown glass. Infra-Bar total transmission of radiant energy is 55%.

Infra-Bar

general wear lenses
that provide

HIGH VISIBILITY
plus
INFRA-RED ABSORPTION

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Infra-Bar FEATURES—

1. Excellent for night driving. Protects from glare and provides high visibility comparable to white lenses.

2. Excellent for daytime use. Absorbs infra-red.

3. Excellent for students, proofreaders, doctors, nurses, technicians, dieticians and others whose eyes are continually exposed to highly reflective or white surfaces.

4. Excellent for color perception. Relative natural colors are retained.

5. Excellent cosmetic appeal. Distinctive aqua color styling is complimentary to wearer.

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INFRA-BAR is available in:

- Corrected Curve Single Vision
- Straight Top Bifocals and Trifocals
- Round Segment Bifocals

Titmus Optical Co., Inc.
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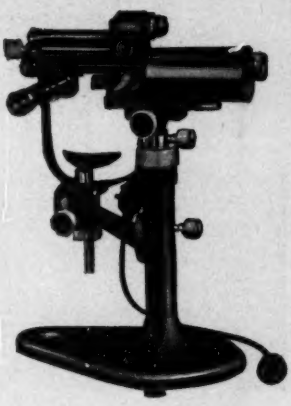
Really **dependable**

THE NEW Rodenstock EYE-REFRACTOMETER



For the objective determination of the refraction of the human eye, permitting instantaneous reading of spherical and cylindrical refraction of any eye, including inclination of axis.
It enables objectively to diagnose quickly and accurately problem and difficult cases like children, illiterates, etc., or cases with pin hole pupils, with a range from plus 20.0 D. to minus 20.0 D.

Rodenstock VERTEX REFRACTIONOMETER

- * Range from plus 25.0 D. to minus 25.0 D.
- * Fast, accurate, advanced optics with sensitive test-mark
- * Read power, axis, prism, prism base at a glance in the field-of-view of the ocular, simultaneously focusing the test-mark
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Extensive evidence based on three years' clinical experience has shown that CORTONE controls both objective and subjective manifestations of rheumatoid arthritis in virtually all cases; in many of these patients, CORTONE has been used for prolonged periods of time.

It is reassuring to note also that the administration of CORTONE does not necessitate any measures that are not readily available to the physician in everyday practice. The use of simple laboratory tests (sedimentation rate, urinalysis, blood count, blood pressure, and recordings of weight), individualized adjustment of dosage, and careful clinical observation will permit most patients to benefit materially . . . without fear of undesired effects.

CORTONE PRODUCT FORMS:

ORAL—Cortone Acetate Tablets, 25 mg. each, bottles of 40 tablets.

PARENTERAL—Cortone Acetate, Saline Suspension for injection, vials of 20 cc., each cc. containing 25 mg.

Literature on Request

Cortone®* *CORTONE is the registered trade-mark of Merck & Co., Inc. for its brand of cortisone.*

MERCK

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Cortone®
ACETATE
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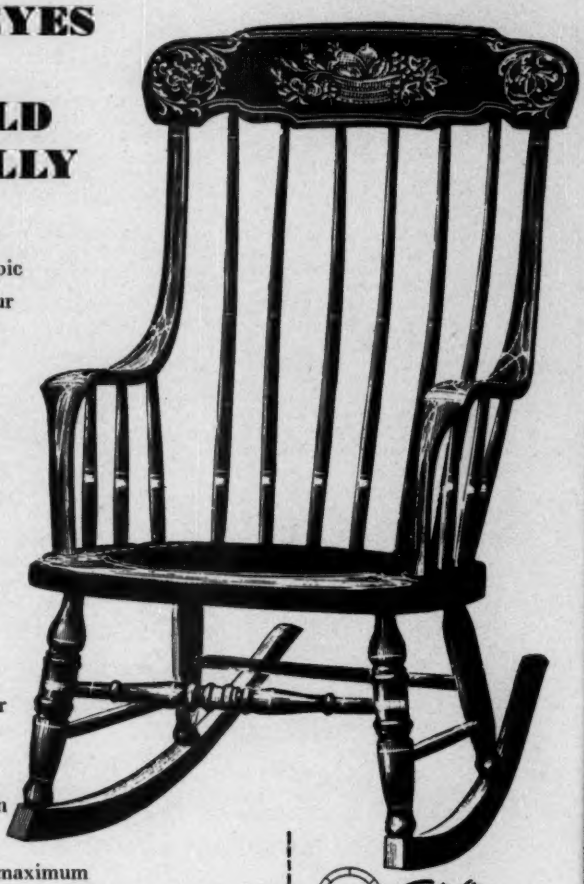
FACTS OF LITE on PRESBYOPES

HELPING EYES *to* GROW OLD GRATEFULLY



Comfort counts with presbyopes! Anything you add to the presbyopic Rx for extra comfort adds to your professional prestige.

Every pair of (presbyopic) eyes is different — some eyes can take it, some *cannot!*

Absorptive lenses are different, too — only true Soft-Lite passes the Comparator Test in which ordinary tints turn dark. Light-sensitive elderly eyes grow old gratefully when the comfort of Soft-Lite is specified on bifocal or trifocal prescriptions. Surrounding excess light is absorbed — while full transmission at the near point is provided through the white segments. For maximum efficiency in presbyopic cases, specify Soft-Lite!

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Soft-Lite Lenses

Featured in Panoptik and S-T Bifocals

some eyes can take it

...some eyes cannot!

Enlarged to show mesh

Exact size

THE NEW CUTLER-HAMBLIN ALL TANTALUM IMPLANT

The latest Cutler Implant for use in enucleations, re-implantations and eviscero-enucleations is described by Dr. Norman Cutler in the February, 1949 issue of the American Journal of Ophthalmology in which he mentions the objectives to be strived for in an ideal implant and prosthesis.

Hamblin's model illustrated herewith is made entirely of Tantalum (a completely inert metal) thereby overcoming the many disadvantages of one made wholly or partly of Plastic. The total weight is 4.3 grammes.

As will be seen in the illustrations, it consists of a ball measuring 17.5 mm. in diameter and 15.5 mm. deep. On the anterior surface is a raised area 12 mm. in diameter and 1 mm. deep, which makes the anterior-posterior length 16.5 mm. The implant is made purposely this size to replace the amount of volume necessarily lost in the removal of the globe and to provide the normal centre of rotation for the prosthesis.

The anterior convex surface of the implant is covered with a fine mesh of tantalum wire behind which is a space sufficient to permit the easy passage of curved suture needles. The adoption of the mesh is the chief feature of the new implant, and the enlarged picture shows the formation of this mesh, which not only offers a larger area for fixation of tissue to the implant but also makes for simplicity in the operation of suturing and more certainty in the fixation.

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WITH PRISMS 28 x 30 MM. SQUARE
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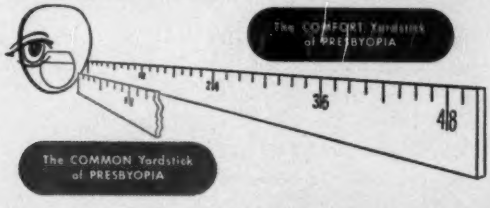

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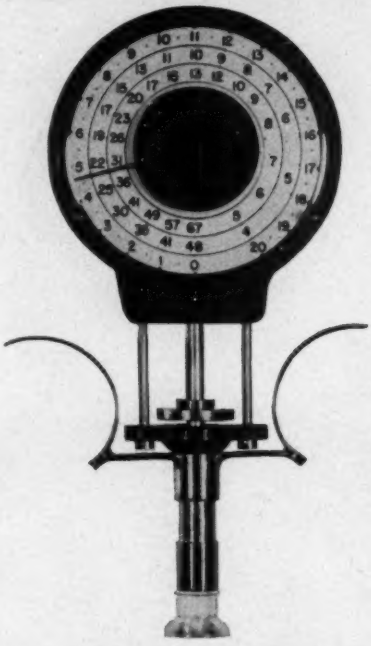

The New

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This is an extremely accurate instrument.

The dial has three scales, the outer being the expanded Schiotz scale, 0 to 20, the middle and inner scales being direct readings in millimeters of mercury for the 5.5 and 7.5 gram weights.

10 and 15 gram weights are included, with conversion table.

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Fully guaranteed

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The improved

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designed by Walter H. Fink, M.D.

This P.C. product is the *only* trial frame made specifically for children. You will find it invaluable for refracting children three years of age and under.

note these advancements!

- ✓ New temple style—easier to slip on, holds frame firmly.
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- ✓ More comfortable for the child.

Complete description and detailed information upon request.

Write today for folder "Trial Frame for Small Children."

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Some Like 'em Straight . . . Some Like 'em Curved . . .

. . . That's so in Baseball . . . from Sand-lot players to Big League Stars

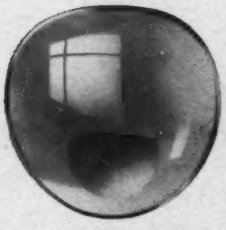
Among the Professions, when it comes to a choice of segment-tops in AO Tillyer Bifocals, it's likewise a matter of preference. Straight or curved, they're both good.

In AO Bifocals, you'll find *curved-top* segments in the famous *Tillyer Ful-Vue*, the most versatile bifocal available on Rx today. When you prescribe them, *specify them as Ful-Vue "C."*

If your preference is for a straight-top segment, and you want a bifocal with ample room for decentration, AO offers the *Tillyer Flat-Top*. This fine lens *now bears the name Ful-Vue "S."*

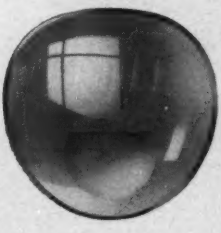
Whichever type of segment you prefer, Ful-Vue "C" and Ful-Vue "S" will prove eminently satisfactory in performance both for your patients and for you.

Recommended for new bifocal wearers because there is a minimum of image jump as the eye travels from the distance to the reading portion. Ful-Vue "C" and Ful-Vue "S" are available through your AO Rx Service.



TILLYER FUL-VUE "C" *(Tillyer Ful-Vue)*

Curved segment top
Optical center 4 mm. below segment top
Segment Height: Maximum 23 mm.
Segment Size: 14 mm. x 20 mm.
Available in White; Cruxite A, AX, D; Calobar C.
On Special Order: Cruxite B, C; Calobar B, D.



TILLYER FUL-VUE "S" *(Tillyer Flat-Top)*

Flat segment top
Optical center 5 mm. below segment top
Segment Height: Maximum 24 mm.
Segment Size: 15 mm. x 20 mm.
Available in White; Cruxite A, AX. On Special Order: Cruxite B, C, D; Calobar B, C, D.

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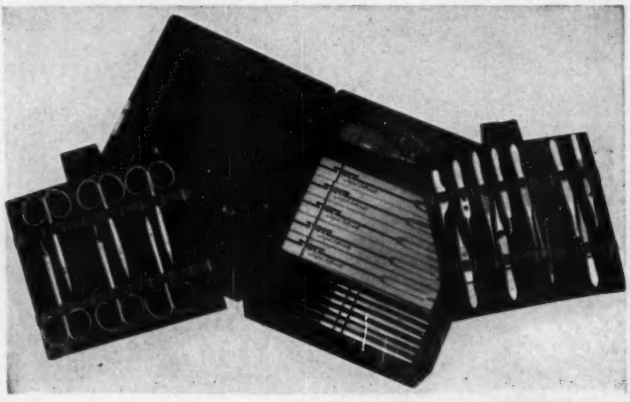

90

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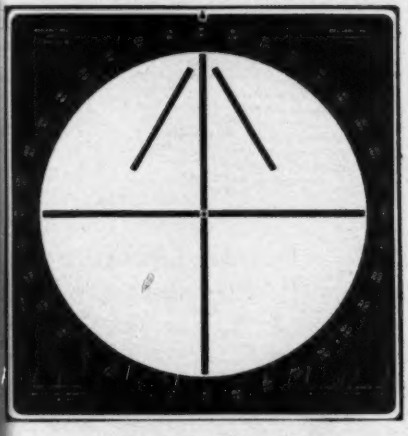

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CONTENTS

PAGE

Competitive Action of Miotics on the Iris Sphincter. KENNETH C. SWAN, M.D., AND LETA GEHRSITZ, M.S., PORTLAND, ORE. ... 477

Studies of Corneal Transparency Under Various Experimental Conditions. K. VAN WALBEEK, M.D., ZAANDAM, NETHERLANDS, AND H. NEUMANN, PH.D., VOORBURG, NETHERLANDS ... 482

Editorial Note. FRANCIS H. ADLER, M.D. ... 488

The Micro-Organisms Causing Sympathetic Ophthalmia. EUGEN SCHRECK, M.D., HEIDELBERG, GERMANY ... 489

Localization of Lacrimal Sac in Dacryocystorhinostomy by Transillumination. LEONARD CHRISTENSEN, M.D., PORTLAND, ORE. ... 501

A Gonioscopic Study of Fistulizing Operations. A. G. DEVOE, M.D., NEW YORK ... 504

Uveitis, Poliosis, and Alopecia in Siblings: A Case Report. WALTER H. BENEDICT, M.D., AND WILLIAM L. BENEDICT, M.D., ROCHESTER, MINN. ... 510

Methods for the Early Diagnosis of Multiple Sclerosis: Observations with Special Reference to the So-Called Ocular Type. OTTO LOWENSTEIN, M.D., NEW YORK ... 513

Corneal Dystrophy Following Secondary Intraocular Operations. PAUL STERNBERG, M.D., AND SAMUEL J. MEYER, M.D., CHICAGO ... 527

Band Keratopathy in Disturbances of Calcium Metabolism. GAYLORD W. OJERS, M.D., AND JOSEPH ALFANO, M.D., PHILADELPHIA ... 531

Studies on the Crystalline Lens: IV. Distribution of Cytochrome, Total Riboflavin, Lactate, and Pyruvate and Their Metabolic Significance. V. EVERETT KINSEY, PH.D., AND CHARLES E. FROHMAN, PH.D., DETROIT ... 536

Experiment in Which Fifty Presbyopes Were Provided with Trifocal Glasses. PAUL W. MILES, M.D., ST. LOUIS ... 542

Adrenergic Blocking Agents in Treatment of Glaucoma. CARROLL R. MULLEN, M.D., AND IRVING H. LEOPOLD, M.D., PHILADELPHIA ... 549

Unilateral Proptosis Due to Fibrous Dysplasia of Bone: Report of Two Cases. CAPTAIN ROBERT B. KING, AND LIEUTENANT COLONEL GEORGE J. HAYES, MEDICAL CORPS, UNITED STATES ARMY ... 553

Localized Injection of the Upper Quadrant of the Bulbar Conjunctiva. ANDREW DEROETTH SR., M.D., SPOKANE, WASH. ... 560

Description of an Ophthalmoscope for Examining the Retina in the Living Eye. H. VON HELMHOLTZ. TRANSLATED FROM THE ORIGINAL GERMAN BY ROBERT W. HOLLENHORST, M.D., SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN. ... 565

REGISTRY OF INTERESTING CASES:

Acute Glaucoma Simulating Acute Iritis. MARVIN POSNER, M.D., BOSTON ... 584

ANNUAL REVIEWS:

Neuro-Ophthalmology. C. WILBUR RUCKER, M.D., ROCHESTER, MINN. ... 586

NEWS AND NOTES ... 599

BOOK REVIEWS ... 600

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COMPETITIVE ACTION OF MIOTICS ON THE IRIS SPHINCTER

KENNETH C. SWAN, M.D.
AND
LETA GEHRSITZ, M.S.
PORTLAND, ORE.

AUTONOMIC drugs may induce miosis by several mechanisms. For example, pilocarpine seems to act directly on the receptor system of the iris sphincter, whereas physostigmine and diisopropyl fluorophosphate (DFP) seem to stimulate contraction of the iris sphincter by an indirect mechanism. Their blocking action on tissue cholinesterases prevents destruction of the physiologically produced acetylcholine, thereby enhancing and prolonging the stimulatory effects of the latter on the sphincter.

It has generally been assumed that a direct stimulating drug, like pilocarpine, and an indirectly acting drug, like physostigmine, have additive effects if administered together because they act by different mechanisms. These drugs are, therefore, frequently used in combination in the treatment of acute glaucoma; however, in patients in whom it was possible to compare treatment responses of the two eyes we have observed that the combined use of these drugs in maximal doses seemed less effective both in degree of miosis and in hypotensive action than the administration of either physostigmine or diisopropyl fluorophosphate alone. We have observed also that the intense spastic action of diisopropyl fluorophosphate on the iris sphincter and ciliary muscles could be modified and made more tolerable to glaucoma patients if large doses of pilocarpine were administered previously. These clinical phenomena suggest that the receptor mechanism of the iris musculature is limited in its ability to react to drug stimulation and indicate that it might be possible for the receptor system to be so tied up with a relatively weak miotic, such as pilocarpine, that reactivity of the muscle to more potent miotics would be reduced. If this fact were established, it would merit consideration in the prescription of miotic drugs to glaucoma patients. It is our purpose to report a series of experiments made to investigate these phenomena under controlled laboratory conditions.

Aqueous solutions containing 4% pilocarpine nitrate effect only moderate miosis when instilled into the conjunctival sac of an albino rabbit, whereas instillations of physostigmine or diisopropyl fluorophosphate produce a strong contraction of the pupil. Nearly ideal circumstances are thereby provided for study of the modifying effects of pilocarpine on pupillary effects of the other miotics, as well as on the light reflex.

This study was made possible by funds given by Mrs. Helen Watzek and sons.

From the Department of Ophthalmology, University of Oregon Medical School.

Presented at the Pacific Coast Section, Association for Research in Ophthalmology, Inc., San Francisco, March 10, 1951.

It has been established that the contraction of the pupil when the retina is stimulated with light is effected through the release of acetylcholine in the iris sphincter. It has been demonstrated also that pilocarpine does not affect the formation of acetylcholine in the tissues or significantly influence the activity of cholinesterases. The influence of pilocarpine on the pupillary light reflex would therefore indicate whether pilocarpine is or is not capable of reducing reactivity of the iris sphincter to acetylcholine. Aqueous solutions of 4% pilocarpine nitrate pooled for several minutes in the conjunctival sac of the albino rabbit consistently induced contraction of the pupil to 4 mm. in the horizontal diameter. This miosis could not be appreciably increased by focusing a strong light on the retina. This light when applied to the untreated (control) eye induced a contraction of the pupil to 2 mm. These experiments, therefore, indicated that pilocarpine in doses sufficient to produce the maximal effects on the pupil reduces reactivity of the iris sphincter of the rabbit to physiologically produced acetylcholine. This action also seems to hold true in the human eye when large doses of pilocarpine are administered. The effect cannot always be demonstrated because nearly maximal miosis is often induced when a large dose of pilocarpine is administered to the normal human eye; however, the miosis may be followed by a mydriasis (so-called paradoxical action of pilocarpine) and a diminished reaction to direct light. This hypoactivity seems a direct effect of the drug on the reactivity of the iris musculature rather than on the sensitivity of the retina, because the consensual reaction of the opposite pupil to light is not affected.

In a second series of experiments, aqueous solutions of 4% pilocarpine nitrate were administered to one eye of rabbits, and then, later, 0.25% physostigmine salicylate ointment was applied topically to both eyes. Variations in pupillary size were recorded. Measurements were made with a transparent rule at a fixed distance from the eye. Illumination of the two eyes was kept constant and at a level which permitted the pupil of an untreated eye to remain moderately dilated.

Pilocarpine was administered by two methods. In one series of experiments, an aqueous solution of 4% pilocarpine nitrate was pooled in the conjunctival sac in contact with the cornea for three or four minutes. In the second, 0.05 ml. of the pilocarpine nitrate solution was injected into the superficial corneal stroma, near the limbus. Miosis was obtained more consistently by the latter method, but light surface anesthesia (one drop of 0.5% tetracaine hydrochloride U. S. P.) was required. To control possible pupillary effects of tetracaine, the instillation experiments were continued. One or two hours after one eye was treated with pilocarpine and its effects had become maximal, 0.01 ml. of 0.25% physostigmine salicylate ointment was placed on the cornea of each eye. The horizontal diameter of the pupils was measured every 15 minutes until the pupils returned to the normal size. Intensity of miosis induced by physostigmine was always less when pilocarpine had been administered previously. When submaximal doses of pilocarpine were followed by the application of physostigmine, further constriction of the pupil occurred in some cases; however, this constriction was not as great and did not last as long as that produced by physostigmine alone. The results of 22 experiments, summarized in Chart 1, indicate that pilocarpine reduces reactivity of the pupil to physostigmine.

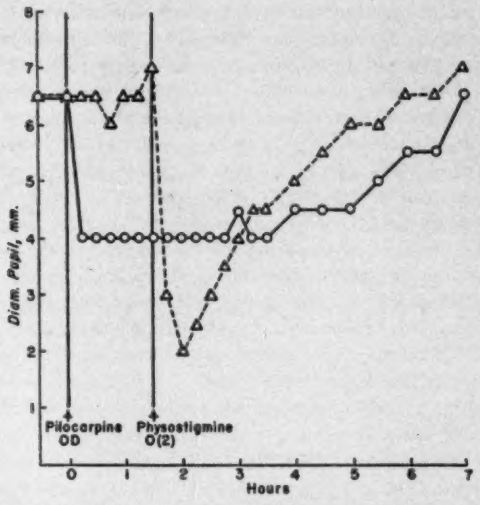

Chart 1.—Degree and duration of miosis induced by physostigmine and by pilocarpine and physostigmine. The values for 4% pilocarpine nitrate and 0.25% physostigmine salicylate used in the right eye are shown by the line with circles; the values for 0.25% physostigmine salicylate used alone in the left eye, by the line with triangles.

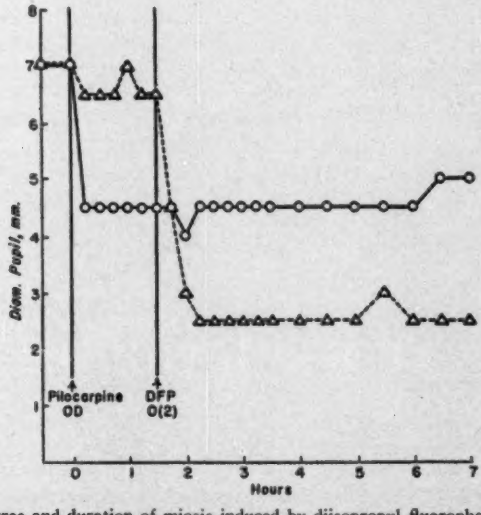

Chart 2.—Degree and duration of miosis induced by diisopropyl fluorophosphate (DFP) and diisopropyl fluorophosphate and pilocarpine nitrate.

The values for 4% pilocarpine nitrate and 0.1% diisopropyl fluorophosphate used in the right eye are shown by the line with circles; the values for 0.1% diisopropyl fluorophosphate used in the left eye, by the line with triangles.

A third series of experiments were conducted to determine the influence of pilocarpine on the miosis induced by diisopropyl fluorophosphate. One or two hours after administration of 4% aqueous solutions of pilocarpine nitrate to one eye, 0.05 ml. of 0.1% diisopropyl fluorophosphate in peanut oil was instilled over the cornea of both eyes. The results of 14 experiments are summarized in Chart 2. They clearly indicate that reactivity of the iris sphincter to diisopropyl fluorophosphate is reduced by prior administration of pilocarpine. The duration of this effect of pilocarpine was determined by other experiments. After a single injection of pilocarpine miosis was observed to persist five to eight hours in the rabbit. With diisopropyl fluorophosphate alone miosis was still evident at 28 hours, but if its application was preceded by the administration of pilocarpine the duration of miosis was reduced to 8 to 20 hours and at no point during this period was it as great as that produced by diisopropyl fluorophosphate alone. Previously administered pilocarpine, therefore, shortened as well as decreased the intensity of miosis induced by diisopropyl fluorophosphate.

In a fourth series of experiments, diisopropyl fluorophosphate or physostigmine was instilled in the conjunctival sac of both eyes of rabbits; then 4% pilocarpine nitrate was injected into the corneal stroma of one eye. If the pilocarpine was injected within a few minutes, maximal constriction of the pupil was only to 4 mm., as compared with 2 mm. on the side treated with diisopropyl fluorophosphate or physostigmine alone. If the pupil was allowed to constrict to 2 mm. before pilocarpine was injected, a transitory, slight dilation of the pupil occurred (1 to 2 mm.). These experiments indicate that pilocarpine administered simultaneously with, or even shortly after, physostigmine or diisopropyl fluorophosphate still reduces reactivity of the iris sphincter to these anticholinesterase compounds; however, the interference is less pronounced than when pilocarpine has been administered previously and its maximal effects established.

COMMENT

In most accounts of ocular pharmacology only the qualitative aspects of the mechanism of action of the autonomic drugs are discussed. These studies indicate that the capacity of the iris muscle to respond to drug stimulation is limited and that that limit can be reached by the local administration of currently available drugs. The quantitative aspects of the action of drugs on the intraocular muscles, therefore, merit attention in clinical ophthalmology.

The exact mechanism by which pilocarpine induces contraction of the iris sphincter has not been determined with certainty; however, like acetylcholine, it seems to have a direct stimulatory action, which is effective even on the denervated muscle. By inhibiting the action of cholinesterase, physostigmine and diisopropyl fluorophosphate indirectly increase the concentration of physiologically released acetylcholine. A decreased effectiveness of these anticholinesterases following the application of pilocarpine is demonstrated in the data presented. This suggests the possibility of competition between pilocarpine and acetylcholine for the receptor substances of the muscle when they are present together. Gradations of this competitive reaction may be assumed from the data.

A basis for these postulations of drug competition can be found in the literature describing the receptor mechanism of the iris sphincter and other muscles. It

should be pointed out that drug "competition" may not be limited to the receptor mechanism of the iris sphincter. Leopold and McDonald [1] have observed that at the time physostigmine binds and inhibits the cholinesterases it also protects these esterases against the destructive action of diisopropyl fluorophosphate; therefore, diisopropyl fluorophosphate has less prolonged effects when physostigmine has previously been administered.

Further studies, including possible stimulating effects of pilocarpine on the iris dilator, will be necessary to determine the mechanism of competition between pilocarpine and acetylcholine, but clinical application need not be deferred. For example, in the medical treatment of acute glaucoma of the narrow-angle, iris-block types, administration of physostigmine alone could be expected to be more effective than the combined use of physostigmine and pilocarpine; however, the combination could be expected to be more effective than pilocarpine alone. Narrow-angle acute congestive glaucoma, therefore, should respond most favorably to administration of physostigmine, or of diisopropyl fluorophosphate without pilocarpine. In the treatment of chronic types of glaucoma different circumstances prevail. The intense spastic action and hyperreactivity of the intraocular muscles induced by physostigmine and diisopropyl fluorophosphate are often discomforting and limit the use of the drug with most phakic patients. With these patients pilocarpine can be used to so modify the action of diisopropyl fluorophosphate that it is well tolerated, but still more effective than other miotics. Preliminary administration of pilocarpine is also useful to minimize discomforting effects when a patient receives the first dose of diisopropyl fluorophosphate.

SUMMARY AND CONCLUSIONS

Combinations of miotics are commonly prescribed with the hope of obtaining more intense miosis and hypotensive effects than could be achieved by the use of a single drug. Data are presented which indicate that, instead of a synergistic or additive action, a weaker miotic may reduce the effectiveness of a stronger drug. Pilocarpine was found to decrease reactivity of the iris sphincter of the albino rabbit to physostigmine and diisopropyl fluorophosphate, as well as to physiologically produced acetylcholine. The exact mechanism of this modifying action of pilocarpine remains to be established, but it is suggested that pilocarpine "competes" with acetylcholine for the receptor mechanism of the iris sphincter.

The results of experiments on the iris of the albino rabbit are in agreement with our observations on glaucoma patients that it is possible to reduce the clinical effectiveness of physostigmine and diisopropyl fluorophosphate by the prior or simultaneous administration of pilocarpine. This modifying action of pilocarpine on the intense spastic and discomforting effects of diisopropyl fluorophosphate is useful when the latter drug is prescribed in the treatment of chronic glaucoma; but in cases of acute congestive glaucoma the stronger drugs should be administered without pilocarpine because maximal miosis is desired.

1. Leopold, Irving H., and McDonald, P. Robb: Di-Isopropyl Fluorophosphate (DFP) in Treatment of Glaucoma: Further Observations, Arch. Ophth. **40**:176-188 (Aug.) 1948.

STUDIES OF CORNEAL TRANSPARENCY UNDER VARIOUS EXPERIMENTAL CONDITIONS

K. VAN WALBEEK, M.D.
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AND
H. NEUMANN, Ph.D.
VOORBURG, NETHERLANDS

FROM previous investigations [1] it is known that corneal transparency is due largely to a certain physicochemical condition of the connective tissue of the cornea. The water content of the corneal connective tissue is regulated by the adjacent living tissues (epithelium and endothelium) which Cogan and Kinsey [1e] showed to be impermeable to chloride and permeable only to water.

Ophthalmologists often observe the great power of the connective tissue of the cornea to absorb water. This power must be ascribed to the absorbing properties of the intermediate substance, which consists chiefly of two components, the collagen and the mucoid. The collagen, split up into loose bundles of fine fibers, lies enmeshed in the mucoid. The mucoid not only fills, as a gel, all spaces between the fiber bundles but also penetrates the bundles and takes part perhaps in the formation of the micelles of the intermediate substance itself. According to Leyns and Gaulhofer,[1h] the two components should be considered separately with regard to their contribution to the total absorptive power of the connective tissue. When dried corneas were exposed to water vapor of increasing concentration, up to a water content of 30%, the water was taken up into the micelles of the collagen, causing a demonstrable expansion of the crystalline lattice (Hertel [1b]). Further water absorption should be ascribed mostly to the interfibrillar mucoid.

The importance of the mucoid for the imbibition of water is also evident from the fact that the absorptive power diminishes greatly if the mucoid is partially extracted with diluted sodium hydroxide solution (Heringa and associates [1f]).

From the Histological Laboratory of the University of Amsterdam.

1. (*a*) Fischer, F. P.: Untersuchungen über Quellungsvorgänge und über Permeabilitsverhältnisse der Hornhaut, Arch. Augenh. **98**:41, 1927. (*b*) Hertel, E.: Anwendung und Bedeutung von Strukturuntersuchungen mittelst Röentgenstrahlen in der Ophthalmologie, ibid. **107**:259, 1933. (*c*) Cogan, D. G.: Experimental Production of So-Called Bullous Keratitis, Arch. Ophth. **23**:918 (May) 1940; (*d*) Bullous Keratitis, with Particular Reference to Pathology of Experimental Corneal Vesiculation, ibid. **25**:941 (June) 1941. (*e*) Cogan, D. G., and Kinsey, V. E.: Cornea: II. Transfer of Water and Sodium Chloride by Hydrostatic Pressure Through Excised Cornea, ibid. **27**:696 (April) 1942. (*f*) Heringa, G. C.; Leyns, W. F., and Weidinger, A.: On the Water Adsorption of Cornea, Acta neerl. morphol. **3**:196, 1940. (*g*) Graubert, D. N.: Étude sur le gonflement du tissu conjonctif, Thesis, Amsterdam, 1948. (*h*) Leyns, W. F., and Gaulhofer, W. K.: Über die Quellung von Bindegewebe bei Formolfixation, Acta neerl. morphol. **2**:345, 1939. (*i*) van Walbeek, K.: De rol van het endotheel en de membraan van Descemet voor de helderheid van het hoornvlies, Thesis, Amsterdam, 1947.

Leyns and Gaulhofer [1h] found that collagen imbibition is intensified by the addition of acid and mucoid imbibition by the addition of alkali. This fact was further worked out by Graubert.[1g] He concluded from the swelling phenomena in solutions of different acids, bases, and buffers that the "acid" swelling (pH less than 4) is a collagen swelling. The "basic" swelling (pH greater than 4) is chiefly a mucoid swelling. Graubert [1g] found that it was the "basic" swelling which was reduced greatly by partial extraction of the mucoid from the cornea.

It is known that in various diseases of the eye turbidity of the cornea is caused by abnormal hydration. Thus, the transparency of the cornea is related to its imbibition.

From the aforementioned observations, it may be expected that the mucoid of the cornea is of great importance to its transparency. This has been demonstrated by the investigations of Leyns, whose results were confirmed by van der Hooff and associates.[2] They showed that the increase in the transparency of the cornea of chick embryos coincides with the appearance of the metachromatic mucoid staining.

The purpose of the investigations published here was to prove experimentally by another means the causal connection between the transparency of the cornea and the imbibition properties of the intermediate substance of the corneal connective tissue. Therefore we made various swelling experiments. We determined the maximum transparency of dried corneas reached by increasing hydration in water, in alkali, in acids, and in salts.

TECHNICAL METHODS

Material.—The investigations were carried out with corneas of cow's eyes, which we obtained from the abattoir. From cow's eyes, as fresh as possible, pieces of cornea were excised with a hand drill (diameter, 13 mm.). Some were dried by the drying-freezing method and kept in a desiccator over concentrated sulfuric acid, and some were used immediately.

Determination of Hydration.—The samples of cornea were immersed in 50 ml. of the test liquid and weighed at regular intervals. The swelling is reported as increase of weight expressed in percentage of dry weight.

Determination of Transparency.—For the transparency measurements we constructed a special holder for the pieces of cornea (Fig. 1). The intensity of the light passing through the lower hole was measured by means of a photoelement connected to a mirror galvanometer. The illuminating current of the source of light was kept constant throughout. In all cases a reading was taken without and with cornea. In all measurements without cornea the deflection of the galvanometer was adjusted to 100 scale divisions by means of a diaphragm. At lower degrees of imbibition we often had trouble with folds produced during drying of the cornea. At higher degrees the unequal swelling (greater at the sides than in the middle) vitiated the measurements somewhat. (Some corneas were useless for transparency measurements, as white patches had developed during the drying process.) In other corneas, more diffuse clouding occurred as a result of drying, so that the discrepancy between duplicate readings was great. For this reason duplicate measurements were sometimes insufficient, and we were obliged to take more readings in order to get a correct estimation of the relation between transparency and imbibition.

RELATION OF TRANSPARENCY TO HYDRATION OF DRIED CORNEAS

Water.—We observed, first, a slight clearing of the cornea, which certainly was not due to smoothing out of the folds. Then a maximum transparency was reached at a water uptake of 200 to 400% of the dry weight. The water content of the

2. van Walbeek, K.; Neumann, H.; Winkelman, J. E.; Ruyter, J. H. C., and van der Hooff, A.: Nadere onderzoekingen over het bindweefsel van het hoornvlies, Verhand. Kon. Vlaamsche Akad. v. geneesk. België **12**:226, 1950.

samples was then approximately equal to that of fresh corneas. According to Duane,[3] this value is 77.7 ± 0.63%, i. e., an imbibition figure based on dry material of 350%. After this a gradually increasing turbidity was seen with further imbibition (Fig. 2).[4]

Alkali.—The swelling in dilute alkali (0.01 sodium hydroxide) showed a somewhat different picture. At first the rate of swelling was larger than the swelling occurring in water in the same period. The alkali extracted from the cornea a considerable quantity of mucoid, which emerged as a slimy mass. Gradually the amount of swelling then became less than that in water, so that after about one hour the degree of imbibition reached in dilute alkali was the same as that in water. Here, also, the maximal transparency was reached at a water uptake of 200 to 400%, i. e., again at approximately the physiological water content (Fig. 2). After this a rather

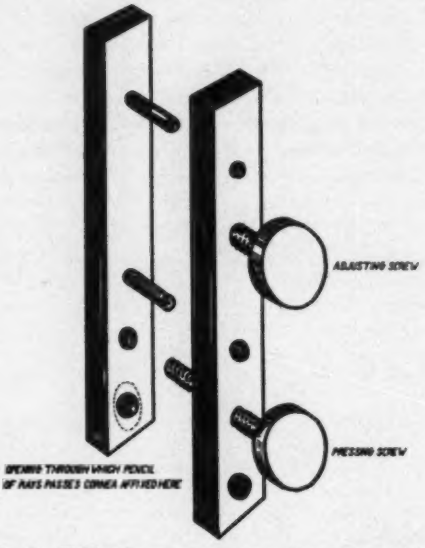

Fig. 1.—Holder for measurements of cornea transparency.

pronounced clouding of the cornea occurred coincidentally with the emergence of mucoid.

Acids.—The swelling in 0.01 N acetic acid lagged far behind that in water and alkali. The clouding increased rapidly. Even when we used rather stronger acid (0.01 N hydrochloric acid) there was a rapid clouding despite the fact that some swelling did take place.

Comment.—From the foregoing experiments we have learned that the maximal transparency of the cornea is reached at about its physiological water content. Moreover, the experiments reported under "Acids" indicate that the water content cannot be the one factor determining the transparency. The increase in transparency

3. Duane, T. D.: Steady State of Corneal Hydration, Am. J. Ophth. **32**:203, 1949.

4. The examination of the cornea with red light, which was tried in order to avoid the difficulties caused by folds, etc., was found to have no particular advantage.

by swelling in acid solution is much smaller than the increase in transparency by corresponding swelling in water or in sodium hydroxide solution. The question arises: To what is this effect of acetic acid and of hydrochloride acid to be ascribed?

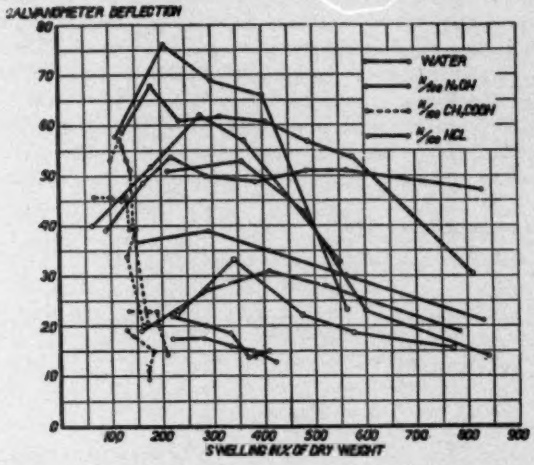

Fig. 2.—Transparency of dried bovine cornea after swelling in various mediums.

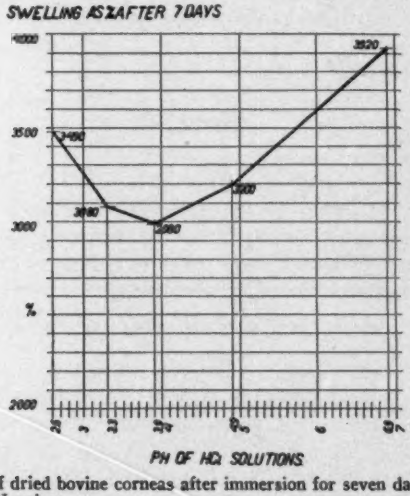

Fig. 3.—Swelling of dried bovine corneas after immersion for seven days in hydrochloric acid solutions of various pH values.

Either both components (collagen and mucoid) or one of them could have been affected by the acid.

As we have learned from previous investigations, the degree of swelling is greatly influenced by the acidity. Swelling is at the minimum at a pH of about 3.9.

This is illustrated in Figure 3, taken from the thesis of one of us (K. van W.[11]). Swelling measurements in buffer solutions gave us similar curves. We were then able to confirm these results (Fig. 4, *not pretreated*). At a pH greater than 3.9 pronounced swelling occurred; at pH values below 3.9 a slower rise was seen. We took then three groups of dried corneas and allowed the first group to swell in MacIlvaine buffers at pH 3.5; the second group, at pH 4.1, and the third group, at pH 4.7 to 4.8. There was no significant difference between the swelling of the first and that of the second group ($293 \pm 11.7\%$ and $290 \pm 9.1\%$). The swelling of the third group was more than that of the other two groups ($351 \pm 13.4\%$). We dried these corneas and allowed two of each group to swell in MacIlvaine buffers at pH values of 3.4, 3.9, 4.0 to 4.1, 4.5 to 4.6, and 5.0. We found that after retreat-

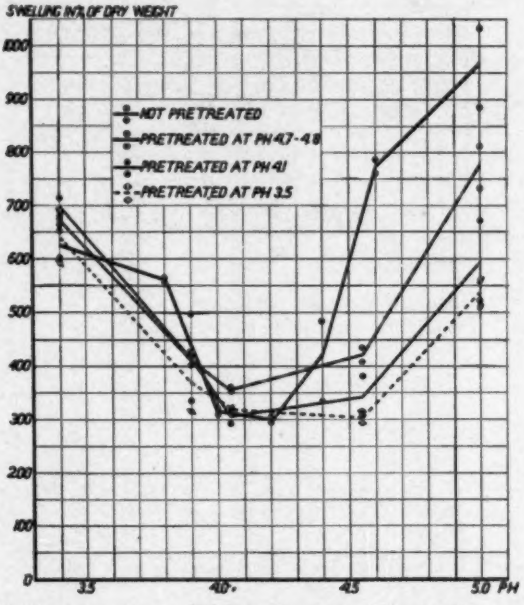

Fig. 4.—Swelling of corneas at different pH values with and without pretreatment.

ment at pH 3.5 the "basic" swelling (pH greater than 4.0) was distinctly reduced. The greatest degree of swelling on the basic side was shown by the corneas pretreated at a pH of 4.7 to 4.8 (citric acid, 0.1 m and sodium biphosphate, 0.2 m). The "acid" swelling was not affected by pretreatment. From the investigations of Leyns[1h] and Graubert[1g] it is known that the collagen swelling is chiefly a collagen swelling; we have shown that the collagen swelling is not attacked but remains unchanged by pretreatment with acids (pH 3.5). We can conclude, therefore, that by pretreatment with acids the collagen is not attacked. It must, therefore, be the mucoid, or a complex in which the mucoid is bound, which is attacked by the acids. This is not inconsistent with the behavior of the corneas treated with "alkali" (pH greater than 4.0).

Salts.—We used solutions of sodium chloride, potassium chloride, and calcium chloride, all equimolecular with isotonic sodium chloride solution. We found that there was no significant difference between the swelling in sodium and that in the potassium chloride (Table). Swelling in calcium chloride was considerably below that in the two other salts after two hours and remained so after 24 and 48 hours. All swellings in salt solutions were considerably below the swelling in water. There was no appreciable difference in the transparency of the corneas which were allowed to swell in potassium, sodium, and calcium chloride. The shape of the imbibition transparency curves was similar to that for swelling in water, with a maximal transparency at about an imbibition of 250 to 400%. The transparency after swelling in calcium chloride solution gave the impression of being less than that after swelling in sodium and potassium chloride solution. Owing to the rather large spread of the transparency figures, the difference, however, appeared not to be significant. Using 0.01 N solutions, we obtained a similar picture, except that the degree of imbibition was slightly larger. It also appears that salts do not have any favoring influence on the slight swelling which the corneas undergo in acids.

Fresh corneas did not give any better reproducibility of the temporary transparency measurements than did the dried corneas. The swelling figures obtained with fresh corneas were, *mutatis mutandis,* the same as those for dried corneas.

Swelling of Dried Corneas in Sodium Chloride, Potassium Chloride, and Calcium Chloride Solutions (Equimolecular with Isotonic Sodium Chloride Solution) After Two Hours

	NaCl				KCl				$CaCl_2$			
Cornea no.	1	2	3	4	5	6	7	8	9	10	11	12
Swelling, in percentage of dry weight	484	563	547	590	556	506	522	516	468	473	403	435

COMMENT

From our previous investigations we concluded that collagen and mucoid were important for the transparency of the cornea. The two components exhibit their own swelling qualities. In their physiological association in the cornea they have a maximal transparency at the physiological water content.

Perhaps the collagen and the mucoid of the cornea are not physicochemically independent but stand to each other in a reciprocal relationship. It is possible that this relationship belongs to the complex type described by Bungenberg de Jong.[5] We intend to continue our research in this direction.

SUMMARY

The transparency of the cornea after swelling in water has been determined in solutions. Here the maximal transparency occurred when the amount of water was 200 to 400% of the weight of the dry matter. This corresponds to the physiological water content of fresh corneas. The mucoid is precipitated by an acid and extracted by an alkali. In both cases clouding of the cornea occurred. Evidently, the mucoid is necessary for the transparency of the cornea. The swelling in salt solutions is considerably less than that in water. The swelling in an equimolecular calcium chloride solution is less than that in sodium chloride or in potassium chloride solution. We suggest the existence of a complex relationship between collagen and mucoid.

5. Bungenberg de Jong, H. G.: Complex Colloid Systems, in Kruyt, H. R.: Colloid Science, ed. 2, New York, Elsevier Pub. Co., 1950.

Editorial Note

The importance of the conclusions drawn in the following paper (The Micro-Organisms Causing Sympathetic Ophthalmia) are obvious. If this work can be confirmed, the riddle of the causation of this dread disease will have been solved, and the search for a preventive or a cure will have been put on a firm etiological basis. It is the policy of the Editorial Board of the A. M. A. ARCHIVES OF OPHTHALMOLOGY to publish only data which are well controlled. In our opinion this criterion has not been entirely fulfilled in this paper. For example, there are no control injections from nonsympathetic cases. This seems particularly important because of the author's suggestion that the organism may lie dormant in the extraocular tissues and be activated when it comes in contact with the uveal tissue.

The conclusions drawn by the author, particularly in connection with the use of antibiotics in eye injuries, are so important, however, that the article is being published at once to encourage comparable investigation by other workers.

FRANCIS H. ADLER, M.D.

THE MICRO-ORGANISMS CAUSING SYMPATHETIC OPHTHALMIA

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IN A FIRST paper,[1] dealing with the nature and the way of migration of sympathetic ophthalmia, I attempted to demonstrate the histopathologic picture in the process by which sympathetic ophthalmia breaks out, persists, and migrates. In sympathetic ophthalmia Type I the seat of irritation and inflammation was found in the lens, the iris, and the ciliary body of the exciting eye, and the specific process was found to proceed from the eyeball as a migrating perivasculitis of the retina and the optic nerve. Analogous to this was the immigration into the sympathizing eye of a periangiitis, which, once it had entered the eye, progressed as a migrating perivasculitis of the retina, leading to anterior uveitis in the sympathizing eye. In Type II sympathetic ophthalmia appears in the exciting eye and, similarly, in the sympathizing eye as an anterior and a posterior uveitis connected by a continuous specific migrating perivascularitis and perineuritis along the posterior ciliary vessels and nerves and along the vessels within the optic nerve. In a later publication,[2] the picture was completed by the histologic study of the eyes and optic nerve of a patient who had died of a cerebral tumor after having had sympathetic ophthalmia for years. Here the continuous migration of the specific process from the exciting eye via the optic chiasm to the sympathizing eye as a perivascularitis and perineuritis could be demonstrated. Furthermore, this publication reported and contained illustrations of microbiological changes in the human eyeball and optic nerve which in size, form, and staining quality were suggestive of the exciting agent of sympathetic ophthalmia. These findings were selectively limited to the histopathologic pathway of sympathetic ophthalmia and were therefore suspected to be of pathogenic character.

In the following report, I shall summarize the experimental demonstration of the micro-organism which I believe causes sympathetic ophthalmia. This was done by passage through chicken eyes and by cultivation of the pathogens on the chorioallantois of chick embryos.

Dr. Schreck is Professor of Ophthalmology.

From Heidelberg University Eye Hospital; Director: Prof. Dr. E. Engelking.

1. Schreck, E.: Über Wesen und Migrations weg der sympathischen Ophthalmie, von Graefes Arch. Ophth. **148**:361-419, 1948.

2. Schreck, E.: Weitere Beiträge zur Frage der Klinik, Mikrobiologie und pathologischen Anatomie der sympathischen Ophthalmie, von Graefes Arch. Ophth. **149**:656-678, 1949.

PASSAGE OF THE EXCITING AGENT OF SYMPATHETIC OPHTHALMIA THROUGH CHICKEN EYES BY USE OF HUMAN MATERIAL

As human donor material, the aqueous of the exciting eye was used twice; the aqueous of the sympathizing eye was used seven times, and the uvea and other contents of the enucleated exciting eye were used three times. It should be mentioned that all human donors clinically showed the typical picture of sympathetic ophthalmia in both the exciting and the sympathizing eye and that the diagnosis was confirmed by histologic examination of the exciting eye.

In the following section examples of both Type I and Type II sympathetic ophthalmia and technical details of the procedure are given.

CASE 1.—A. B., aged 64, had a complicated cataract extraction elsewhere in May, 1949. Five weeks after operation the patient was dismissed, and no glasses were prescribed for the eye operated on, which, according to the patient, had no vision. In July, 1949, inflammation of the second eye was treated by a practitioner. In January, 1950, the patient was admitted to the eye clinic of Heidelberg University. The clinical picture was characteristic of sympathetic ophthalmia, with secondary glaucoma in the sympathizing eye. The exciting eye was enucleated and immediately cut in half. One-half was put in dilute solution of formaldehyde, and histologic examination revealed the typical morphologic picture of sympathetic ophthalmia Type I.

Two factors were found to be of the utmost importance for the successful transfer of the exciting agent of sympathetic ophthalmia: strict sterility, as for any intraocular operation, and constant maintenance of body temperature throughout the procedure. The investigator wore a sterile gown and gloves. All instruments and dishes were sterilized and kept in an incubator at 37 C. The eye was cut in half; one-half of the eyeball was eviscerated and the contents caught in a mortar, which stood in a water bath. Then the contents of the eye—uvea and the remains of vitreous and lens—were homogenized, aspirated into a syringe with approximately an equal amount of isotonic sodium chloride solution, and immediately injected into the right eyes of five chickens.

A paracentesis was performed on the patient's sympathizing eye, which had secondary glaucoma, and the aqueous was used as donor material for passage in chickens (Fig. 2) and for inoculation of the chorioallantois of the chick embryo. The aqueous was aspirated into a tuberculin syringe and mixed with approximately an equal amount of isotonic sodium chloride solution (about 0.2 cc.). Again, the syringe and salt solution, as well as all involved materials, were kept at a temperature of 37 C.

The material was injected either into the vitreous or into the anterior chamber of the chicken eye. When it was injected into the anterior chamber, the lens was scratched slightly.

I shall first review the events which followed the inoculation of the uveal material of the patient's exciting eye into the right eyes of the five chickens (Blue 50, SO4, SO5, SO6, and SO7). The details are given in Figure 1. Under the symbol *R* (right eye) the clinical degree of the uveitis which resulted in the exciting eye is noted; it should be emphasized that in all cases only the right eye was inoculated, whereas the left eye remained untouched. Under *L* (left eye) the clinical degree of uveitis which resulted in the sympathizing eye is noted. Under *A* the severity of the sympathetic ophthalmia as noted histologically is listed both for the right eye and for the left eye. When only a single symbol representing the severity of the uveitis is shown under *RA* or *LA*, it applies to both the clinical and the histologic picture. For the passage of the exciting agent of sympathetic ophthalmia, the contents of one-half of either the exciting or the sympathizing eye was used, whereas the other half was kept in dilute solution of formaldehyde for histologic investigation.

The first passage was performed on Jan. 9, 1950. In this series the donor material of Patient A. B. was injected into both the aqueous and the vitreous of chicken eyes. Later, however, it was found to be sufficient to inject the material either into the vitreous or into the anterior chamber and, at the same time, to scratch the lens. Since the over-all average of the clinically successful transfers was 25%, it was thought advisable to inoculate five chicken eyes at once. A transfer was considered clinically successful when material from a human

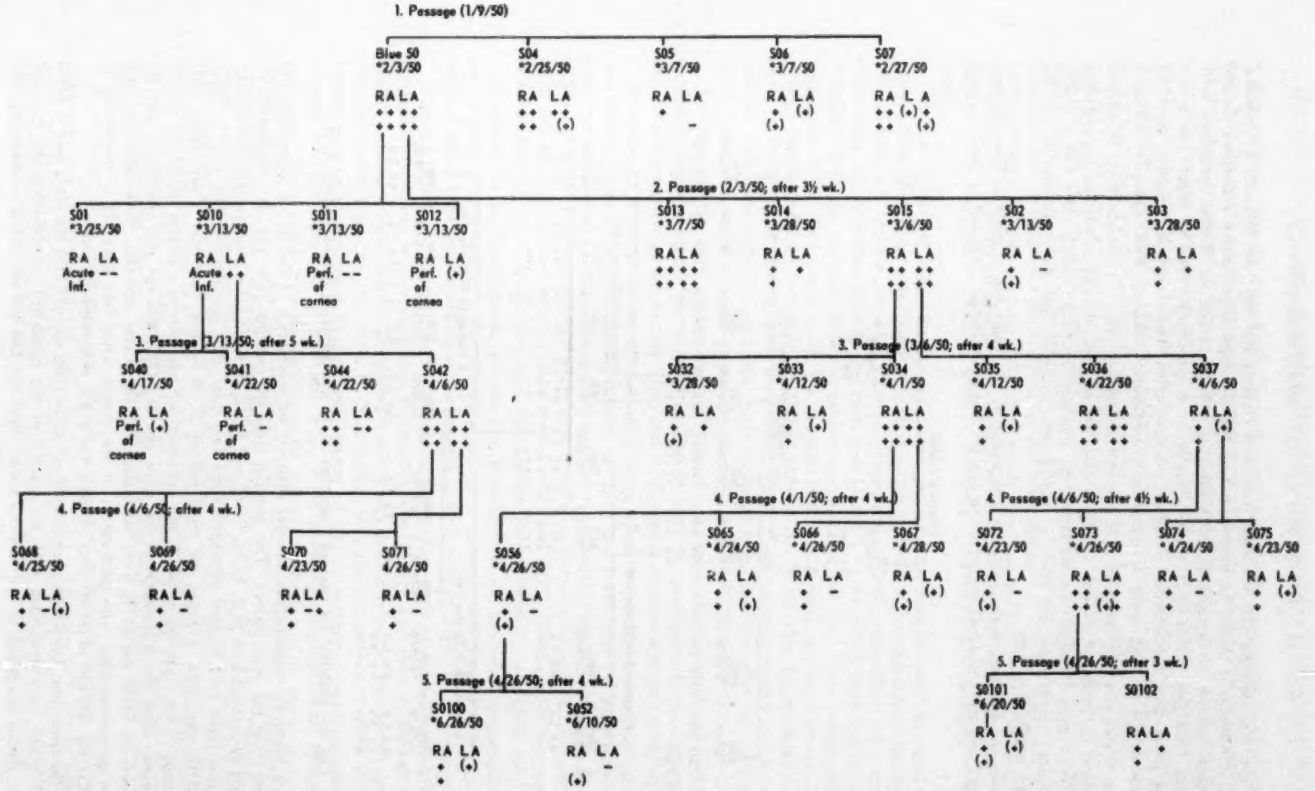

Fig. 1.—Sympathetic ophthalmia, chicken passages. The original material was derived from the exciting eye of Patient A. B. (uvea and intraocular content of the eye). Inoculation was made only into the chickens' right eyes.

In this figure and in figures 2 to 4, *R* indicates the right eye; *L*, the left eye; the asterisk, the date the chicken was killed, and the minus sign, that the chicken died. Under the right and left eyes (*R* and *L*) the clinical degree of chronic uveitis is noted: (+) indicates slight; +, medium; + and (+), strong; ++, massive; under *A* (*RA* and *LA*) the histopathologic degree of the chronic uveitis is noted.

donor eye was injected into the right eye of a chicken and this was followed by bilateral uveitis. However, it should be mentioned that the histologic investigation sometimes showed the typical picture of sympathetic ophthalmia in eyes in which no clinical symptoms were observed. The eyes which were silent clinically were successfully used as donors for a succeeding generation of recipients, in which the eyes often showed uveitis clinically, since the virulence of the exciting agent of sympathetic ophthalmia increased with successive passages.

Two weeks after the inoculation of the first generation (Fig. 1), chicken Blue 50 showed the typical symptoms of chronic uveitis in both the exciting and the untouched sympathizing eye. There were follicular conjunctivitis and abundant discharge, which often had a chalky consistency; precipitates, and fibrin in the anterior chamber, and glassy nodules in the iris near the pupillary margin.

Three and one-half weeks after the inoculation of the right eye of chicken Blue 50, both the right and the untouched sympathizing left eye were enucleated. One-half of each eye was

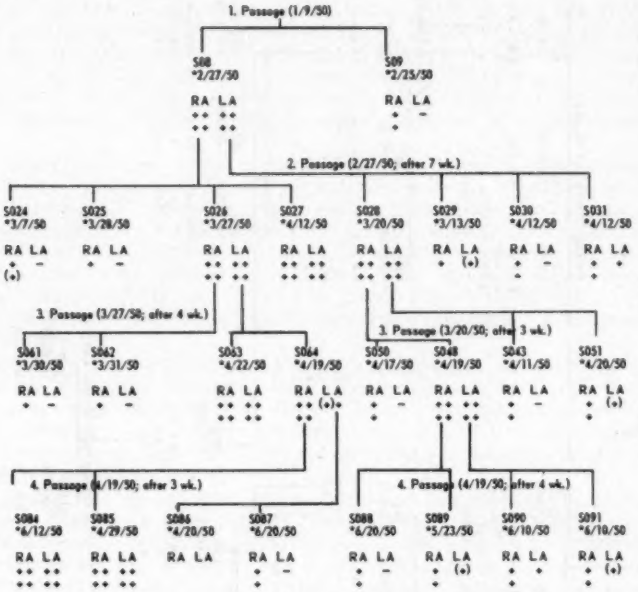

Fig. 2.—Material for passage: aqueous of the sympathizing eye of Patient A. B.

used for histologic examination, whereas material for inoculation of the second generation was obtained from the other halves. The material from the exciting right eye was inoculated into the right eyes of chickens SO1, SO10, SO11, and SO12. Here infection was involved, and all four inoculated right eyes showed panophthalmitis two days after inoculation. The eyes of SO11 and SO12 were lost, whereas the right eye of SO10 became quiescent. Four weeks after inoculation of the right eye of SO10, the untouched left eye showed a picture of chronic uveitis. Five weeks after the inoculation of the right eye of SO10, this eye was enucleated, and the right eyes of SO40 and SO41 were inoculated with the ocular material. Both inoculated eyes showed panophthalmitis with perforation of the cornea after two days. It is interesting to note that the left eye of SO40 later showed low-grade sympathizing uveitis.

At the same time, five weeks after inoculation of the right eye of SO10, the right eyes of SO44 and of SO42, were inoculated with the content of the untouched sympathizing left eye, and chronic uveitis developed in both the inoculated right eye and the untouched sympathizing eye

of these chickens. This third generation, as well as the fourth generation, which received material from both the exciting and the sympathizing eyes of SO42, showed clinically and histologically the typical picture of sympathetic ophthalmia. The fact that the right eye of SO10 exhibited an acute purulent infection, whereas the left eye of SO10 showed merely the typical chronic uveitis, which then was successfully transferred to two more generations, suggests that the exciting agent of sympathetic ophthalmia is separated from the bacteria causing acute infection of the right eye by traveling from the exciting eye over the optic chiasm into the sympathizing eye.

Four weeks after inoculation of the right eye of SO42 the contents of this eye were injected into the right eyes of SO68 and SO69, in a fourth passage. The contents of the untouched sympathizing eye of SO42 were inoculated into the right eyes of SO70 and SO71. In all the inoculated eyes the typical uveitis developed, and also appeared in the left eyes of SO68 and SO70. However, all four chickens died approximately three and one-half weeks after inoculation, indicating the increasing virulence of the exciting agent of sympathetic ophthalmia with further passages. The morphologic changes noted in the various organs will be published in a later paper.

Thus far, I have discussed the passages which started with material from the right eye of chicken Blue 50. Let us now follow the left eye. The material of the untouched sympathizing left eye was used for five successful passages. Three and one-half weeks after the inoculation of the right eye of chicken Blue 50, the right eyes of SO13, SO14, SO15, SO2, and SO3 were inoculated with the material of the untouched sympathizing left eye. Four weeks after the inoculation of the right eye of SO15, the material from this exciting eye was used for a third passage into the right eyes of SO32, SO33, and SO34. Four weeks after the inoculation of the right eye of SO34, the material from the exciting eye of SO34 was injected as a fourth passage into the right eyes of SO56 and SO65. Four weeks after the inoculation of the right eye of SO56, material was used as a fifth passage into the right eyes of SO100 and SO52.

Returning to the third passage, let us follow the material which was obtained from the untouched sympathizing left eye of SO34 four weeks after the inoculation of the exciting right eye. As a fourth passage, the eyes of SO66 and SO67 were inoculated with this material.

Returning to SO15, in the second generation, let us follow the passage of the material which was obtained from the untouched sympathizing left eye, four weeks after the inoculation of the right eye of SO15. As a third passage this material was injected into the right eyes of SO35, SO36, and SO37. Four and one-half weeks after inoculation of the right eye of SO37 the material from this eye was injected into the right eyes of SO72 and SO73. Three weeks later material from the right eye of SO73 was used for a fifth passage into the right eyes of SO101 and SO102.

Returning to the third passage, we note that material from the untouched sympathizing left eye of SO37 was injected as a fourth passage into the right eyes of SO74 and SO75, four and one-half weeks after the inoculation of the opposite, exciting eye of SO37.

Figure 1 presents an example of the passages of the exciting agent of sympathetic ophthalmia in which the material was obtained from the exciting eye. Figure 2 presents an abstract of the passages of the exciting agent of sympathetic ophthalmia derived from the aqueous of the sympathizing eye of the same patient, A. B. This passage was also started Jan. 9, 1950, when the human aqueous was mixed with an equal amount of isotonic sodium chloride solution and injected into the right eyes of SO8 and SO9. Four consecutive passages were successfully performed. The material from the exciting right eye was used after seven weeks as a second passage. A third passage was made four weeks after the second from both an exciting and a sympathizing eye. Three weeks after the third passage the material was transferred as a fourth passage again from both the exciting and the sympathizing eye. Seven weeks after the inoculation of the exciting right eye of SO8 in the first passage, material was obtained from the untouched sympathizing eye and used as a second passage. Three weeks after this second passage the third passage was performed, and four weeks after the third passage a fourth passage was performed. In all instances the material of both the untouched sympathizing eye and the exciting eye was used.

CASE 2.—M. G., a white man aged 64, had a venous thrombosis in January, 1950, and an iridectomy was performed on the right eye for secondary glaucoma. Four weeks after the operation uveitis of the untouched left eye developed, and the patient was admitted to this hospital. The clinical symptoms were typical of sympathetic ophthalmia in both the exciting and the

sympathizing eye. The diagnosis was confirmed by the histologic picture of the exciting eye, on enucleation, which was that of Type II sympathetic ophthalmia. Figure 3 presents in brief form the three passages of the exciting agent of sympathetic ophthalmia Type II derived from the contents of the exciting eye.

Figure 4 presents a summary of the four passages of the exciting agent of sympathetic ophthalmia derived from the aqueous of the sympathizing eye of M. G. From all eyes listed in Figures 1, 2, 3, and 4, material was used for inoculation of the chorioallantois of the chick embryo.

Generally speaking, human uveal material from the exciting eyes and human aqueous from both the exciting and the sympathizing eye, as well as uveal material and aqueous from exciting and sympathizing chicken eyes, were successfully used in consecutive passages of the exciting agent of sympathetic ophthalmia up to five generations. In one instance a successful sixth passage is still going on. After inoculation either of the aqueous, with scratching of the lens, or of the vitreous, the ensuing sympathetic ophthalmia may be transmitted to the untouched left eye in as early as nine days, but usually it is noted only after two to six weeks. In the manner

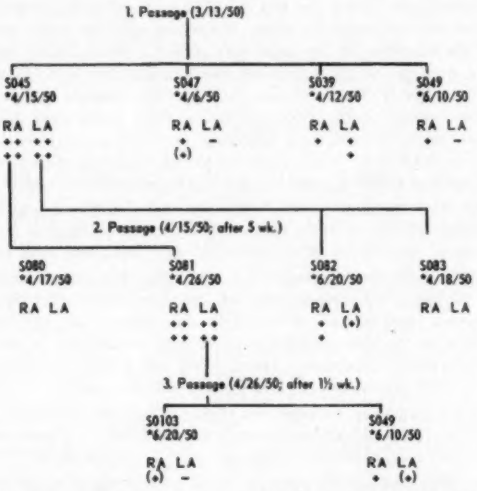

Fig. 3.—Material for passage: uveal tissue and isotonic sodium chloride solution from the exciting eye.

described above, 121 chickens have been inoculated thus far. With successive passages the sympathetic infection has become more virulent. Thus, the symptoms of the chronic uveitis appeared earlier and were more massive in the inoculated right eye, as well as in the untouched left eye. The transmission to the untouched left eye took place more rapidly. On the conjunctiva appeared large follicles, which abundantly produced a peculiar chalky secretion of dense consistency. The death rate among the chickens rose, the cause of which will be discussed in a future publication, concerned with the changes found in organs other than the eye. The increased virulence also was demonstrated when the chorioallantois of chick embryos was inoculated with the material. The exciting agent developed more rapidly, and a denser and more extensive invasion of the agent into the cells of the ectoderm took place. A heavier and more extensive periangiitis migrans occurred in the mesodermal stroma. In rare cases infiltration of the endoderm of a speckled type was observed.

In a few chickens the method which was used failed to elicit a chronic uveitis either in the inoculated right eye or in the untouched left eye, even after repeated inoculation. Therefore these chickens might be regarded as being resistant, and possibly immune, to the sympathetic infection.

Intraocular inoculation of pigeons, rabbits, and guinea pigs was carried out in the same manner. The results of all inoculations were negative, even when material was used which had already gone through chicken passages and thus was believed to have a higher virulence.

The susceptibility of the chicken to the agent of sympathetic ophthalmia raises the question, Does the chicken commonly act as its host? The negative results of all other animal intraocular inoculations make it probable that no other pathogenic organism was involved. The bacteriologic controls on the usual culture mediums consistently remained sterile. As a control, chorioallantois of the chick embryo was

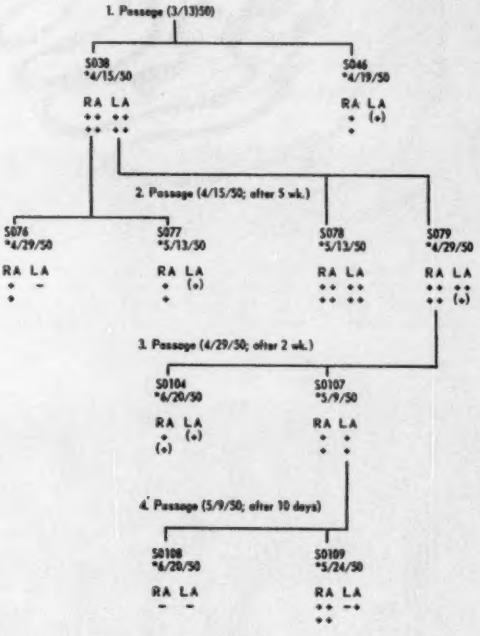

Fig. 4.—Material for passage: aqueous and isotonic sodium chloride solution from the sympathizing eye.

inoculated solely with a sterile isotonic sodium chloride solution which was used for routine dilution of the inoculation material. Here, too, no growth was obtained.

Microscopic Picture of the Chicken Passages

Histologic study of the visual organs inoculated with sympathetic ophthalmia enables one to pursue certain histopathologic and bacteriologic questions.

In the animal experiments described, it was possible to reproduce the histopathologic picture of the onset and migration of sympathetic ophthalmia, as previously described in the human eye. It consisted of a specific migrating periangiitis and perineuritis. The process was demonstrated as a continuous one, starting from the exciting eye and traveling over the chiasm to the sympathizing eye. This is illustrated by Figure 5, showing a pecten which seems to be particulary significant

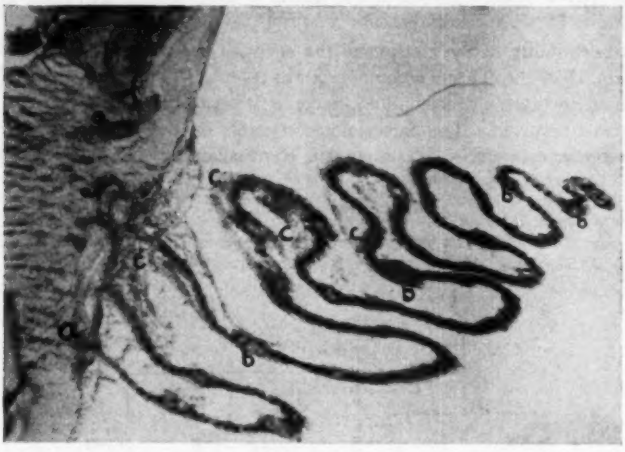

Fig. 5.—Pecten of the sympathizing (untouched) eye of a chicken passage, with migration of the sympathetic ophthalmia from the sympathizing eye over the optic nerve and the chiasm as periangiitis migrans. The infiltration of the migrating process surrounds the central vessels of the optic nerve (*a*) and the vessels of the pecten (*b*). Invasion of the vitreous by the specific infiltration is shown at *c*.

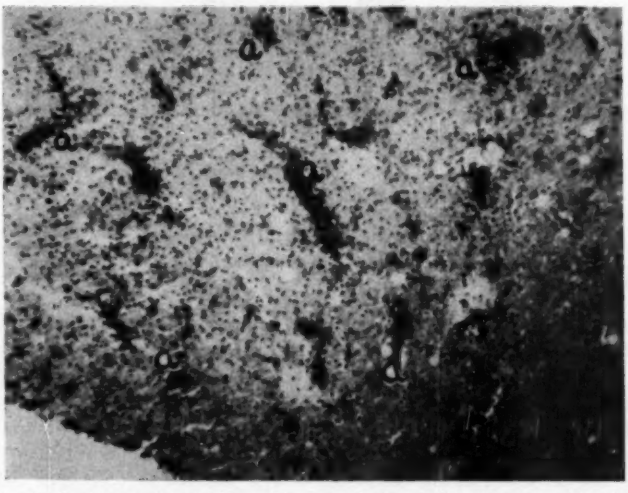

Fig. 6.—Optic chiasm of a chicken with sympathetic ophthalmia produced by inoculation, showing characteristic periangiitis migrans (*a*). See Figure 7.

for the initiation of sympathetic ophthalmia in the chicken, for its emigration from the exciting eye, and for its immigration into the sympathizing eye. Figure 6 shows the chiasm, which is entirely crossed in the chicken. Its entire cross section is dotted with numerous perivascular cellular cuffs, which decrease in density as they approach the cerebral side. With few exceptions, they were completely lacking in the brain.

The experiments further provided information regarding the bacteriologic problem. As already mentioned, an organism in the human eye has been described previously which is suspected of being the exciting agent of sympathetic ophthalmia. This organism can also be seen in the histologic sections of the chicken eye, in the eyeball and the orbit of the exciting and the sympathizing eye, and in the entire optic nerve and the chiasm. These micro-organisms are seen only in certain selective areas—the adventitial cells of the vessels and the nerves, the perivascular and peri-

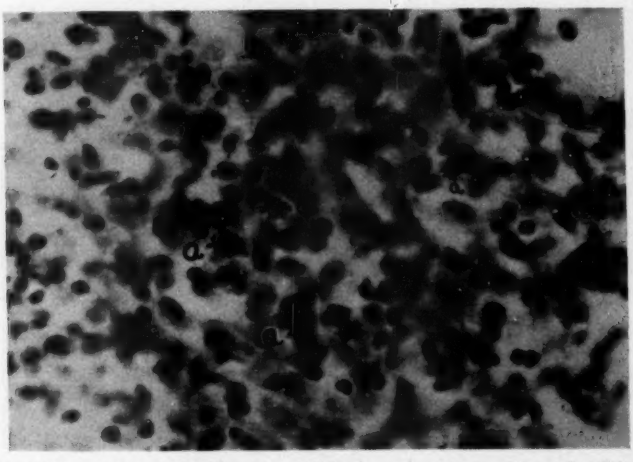

Fig. 7.—High-power magnification of a chicken's optic chiasm with periangiitis migrans sympathicans (same preparation as that shown in Figure 6). The micro-organisms appear as small dots.

neural tissue spaces, and their border cells. The micro-organism can be recognized in Figure 7, which is a high-power magnification of the periangiitis migrans in the chiasm shown in Figure 6.

The extraocular transmission of the infective agent of sympathetic ophthalmia elicited changes in various organs of the test animals, and the infective organism was seen in the histologic preparations. Thus, intranasal inoculation of mice and rats produced a fibrinohemorrhagic, usually nonfatal, pneumonia with invasion of the lungs. Intracerebral inoculation of mice produced a circumscribed periangiitis migrans of the brain and meninges, with few pathogens, sometimes accompanied with chronic uveitis of both eyes. Intraperitoneal inoculation of guinea pigs and rats resulted in moderate perivasculitis of the liver, in which pathogens were seen. A similar condition occurred in mice and rats fed inoculating material. The perivasculitis spread over the intestinal tract. However, there was no orchitis, for the infective agent does not invade the tunics of the testis.

GROWTH OF EXCITING AGENT OF SYMPATHETIC OPHTHALMIA ON CHORIOALLANTOIS OF THE CHICK EMBRYO

Fresh chicken eggs were kept in the incubator at 37 C. and were ready for inoculation of the chorioallantois after nine to fourteen days if the embryo was alive. A total of 217 inoculations were performed, mostly after incubation of the eggs for 11 days. If the prescribed precautions are observed, inoculation of the chorioallantois of chick embryo is almost invariably successful. I repeat that the exciting agent of sympathetic ophthalmia is very sensitive to a change of temperature, which therefore must be kept at 37 C. throughout the procedure. Experiments are at present under way to establish the range within which the temperature, the amount of isotonic sodium chloride solution with which the inoculating material is mixed, and other factors may be varied. It may be mentioned that human material kept in a closed ampule for 10 days in an incubator at 37 C. was successfully used as donor material.

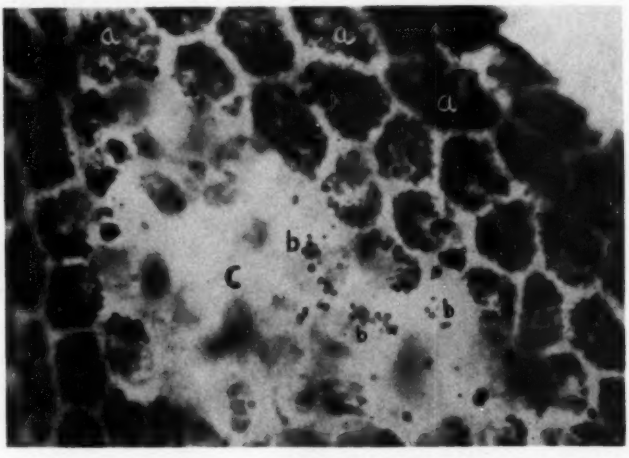

Fig. 8.—Growth of the pathogen of sympathetic ophthalmia by inoculation of the chorioallantois of a chicken embryo; progressive migration into the cells of the ectoderm, which are filled with numerous pathogens (*a*). Free, migrating pathogens are indicated by *b*; the mesoderm is designated by *c*.

The actual inoculation with the donor material of the chorioallantois of the chick embryo does not differ from the standard method commonly used in inoculation of the chorioallantois with rickettsias. One-half the inoculated eggs were used as new donor material and one-half for histologic study two to seven days after inoculation. The chorioallantois of the chick embryo appears in paraffin sections as a manifold membrane between the outer ectoderm and the inner endoderm, between which is the mesoderm. After inoculation the exciting agent of sympathetic ophthalmia invaded cell after cell of the ectodermal membrane (Fig. 8). In the mesoderm, the exciting agent of sympathetic ophthalmia spreads and forms the characteristic picture of migrating periangiitis, with infiltration of the adventitial cells of the blood vessels and the border cells of the perivascular tissue spaces (Fig. 9). In rare cases some cells of the endoderm showed invasion of a speckled type, which was believed to be a sign of particular virulence.

These results are based upon observations on 217 inoculations of the chorioallantois of the chick embryo. The human material was obtained from the aqueous of two exciting eyes, the aqueous of seven sympathizing eyes, and the uveal tissue of three exciting eyes. The rest of the inoculating material was derived from chicken eyes, either the aqueous or the uveal tissue of the exciting or sympathizing eye being used.

Furthermore, transmission was successful from an infected chorioallantois, as donor, to another chorioallantois, as recipient, in repeated succession and finally back from the chorioallantois into a chicken eye.

With exactly the same technique, isotonic sodium chloride solution and various unrelated materials were inoculated, but in no instance was growth of the microorganism observed. The inoculation material for the controls was derived 26 times from the aqueous and 22 times from ground uvea of eyes which had perforating

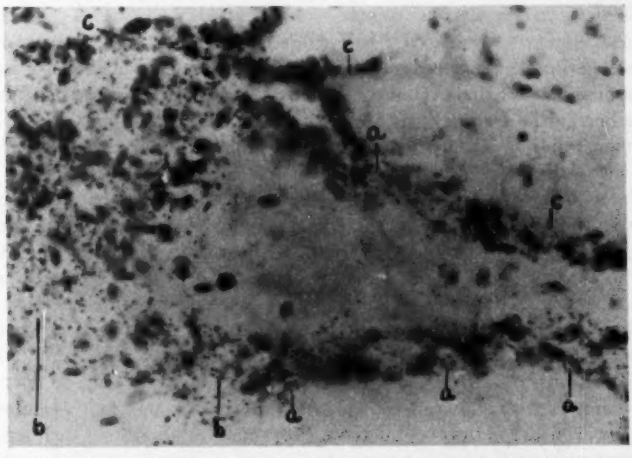

Fig. 9.—Migration of the specific process in the mesoderm of the inoculated chorioallantois as typical periangiitis migrans, with numerous pathogens in the adventitial cells of the vessels (*a*), free in the perivascular tissue spaces (*b*), and in their border cells (*c*).

injuries with suspected sympathetic ophthalmia, but without involvement of the second, uninjured eye. Aqueous was derived twice, and ground uvea five times, from eyes with intraocular tumors. Ground uvea from eyes with corneal staphyloma was used 6 times, the aqueous of eyes with herpetic iritis 3 times, and conjunctival material from various types of conjunctivitis, 14 times.

CONCLUSIONS CONCERNING THE HISTOLOGY OF HUMAN SYMPATHETIC OPHTHALMIA

Based on a review of the histologic preparations in 54 cases of sympathetic ophthalmia published in previous papers in the light of the foregoing experiments, a summary of the situation follows:

The exciting agent of sympathetic ophthalmia remains stationary as a saprophytic, harmless parasite in the conjunctival sac, in its epithelial cells, in the adventitial cells of the conjunctival and episcleral vessels, and in the vessels of the limbal

arcade. Furthermore, the parasite remains in the endothelial cells of Tenon's capsule. Only when the micro-organism comes in contact with uveal tissue does it become virulent and pathogenic. This can happen whenever the corneoscleral barrier is opened, e. g., by a perforating injury, operation, or perforating malignant intraocular tumor, in which event the uveal tissue becomes exposed. Inoculation of the lens with the organism causes sympathetic ophthalmia Type I, with anterior uveitis and migrating periangiitis of the retina and the optic nerve. Invasion of the infective agent into the uveal tract, which has been exposed, produces sympathetic ophthalmia Type II, with anterior and posterior uveitis and migration of the pathogen as periangiitis and perineuritis along the ciliary nerves and the optic nerve. This opinion is based on the histologic examination of 47 exciting and 7 sympathizing eyeballs and 1 human optic chiasm. Sympathetic ophthalmia after evisceration of the eyeball, after subconjunctival rupture of the globe with intact conjunctiva, and in connection with malignant choroidal tumors can now be better understood.

CLINICAL APPLICATIONS

The experiments reported in this paper showed that the micro-organisms causing sympathetic ophthalmia could consistently be grown on the chorioallantois of the chick embryo if the material was derived from human aqueous. The pathogen was also demonstrable by inoculation of chicken eyes. It is suggested, therefore, that use be made of these facts by performing a diagnostic puncture of the anterior chamber of an eye suspected of having sympathetic ophthalmia and immediately inoculating the warm material on the chorioallantois of chick embryos, as described above. In view of the general experience with Rickettsia group of organisms, to which the exciting agent of sympathetic ophthalmia seems to be related, not much help can be expected from the sulfonamides and penicillin. One must keep in mind that if penicillin or streptomycin is added to a fixed flora, bacteria are separated from rickettsias, the former being destroyed and the latter allowed to multiply virulently. On the other hand, it would seem worth while to try aureomycin, chloramphenicol (chloromycetin®), *P*-aminobenzoic acid and *P*-aminosalicylic acid. However, the old proved methods keep their validity, viz., early enucleation of the suspected eye, not evisceration of the eyeball, and treatment with methenamine sodium salicylate (cylotropin®) and atophanyl® (a preparation of cinchophen sodium, sodium salicylate, and procaine hydrochloride).

SUMMARY

The exciting agent of sympathetic ophthalmia was demonstrated by consecutive passages through chicken eyes and by growing it on the chorioallantois of chick embryos. Inoculations were made into the right eyes of 121 chickens, and material from both the inoculated right eyes and the untouched sympathizing left eyes was obtained for succeeding passages. In all, 217 inoculations of the chorioallantois of chick embryos were performed. As human donor material, the aqueous of exciting eyes was used twice, the aqueous of sympathizing eyes, seven times, and uveal material from exciting eyes, three times.

LOCALIZATION OF LACRIMAL SAC IN DACRYOCYSTORHINOSTOMY BY TRANSILLUMINATION

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THE ANATOMICAL peculiarities of the nasolacrimal sac and duct have placed the ophthalmologist in a position of disadvantage when faced with surgical repair of obstructions in this system. Being relatively unfamiliar with the nasal passages, he has by necessity had to devise surgical corrective procedures based on an external approach. Although this approach is generally successful, there are several disadvantages, such as occasional scarring of the skin, disruption of the medial canthal ligament, and distortion of the sac in its bony fossa. In addition, there is often extensive bleeding during the procedure. The approach

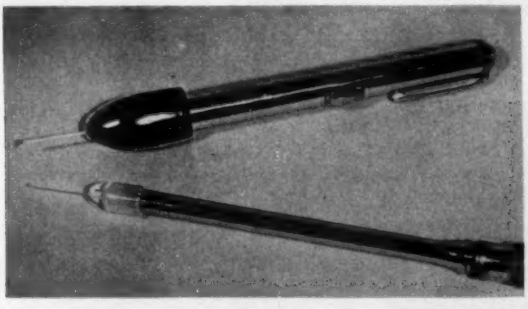

Fig. 1.—The upper probe has a blackened hilt to block out all extraneous light and is constructed to fit a small flashlight. The lower probe is attached to an electric fixture and has more intense and even illumination.

from the nasal cavity has none of these disadvantages and seems more physiologic. In this operation anatomical disturbances are limited to the establishment of a communication between the sac and the nasal cavity. The advantages of this internal approach have long been recognized. Using this method, Jones and Boyden [1] have recently reported an extremely high percentage of successful results in a large number of cases; however, it poses the problem of accessibility. To one familiar with the landmarks of the nasopharynx this approach usually offers little technical difficulty, but to the ophthalmologist, who is relatively unfamiliar with the anatomy of the nose and the use of the head mirror, the problem is somewhat formidable.

From the Department of Ophthalmology, University of Oregon Medical School.

1. Jones, Lester, T., and Boyden, Guy M.: The Rhinologists' Role in Tear Sac Surgery, Tr. Am. Acad. Ophth., to be published.

Even to the initiated, anatomical variations in the position and size of the nasolacrimal fossa make it difficult to localize the new aperture in the desired exact position at the most dependent part of the patent canal. Therefore, it was felt

Fig. 2.—Probe in position with tip against the nasal bone.

Fig. 3.—Artist's drawing showing area of illumination in nasal cavity.

that if a simple means of accurate orientation in the nose could be devised this procedure could be made less difficult and would have a much wider application.

Utilizing an old principle based on transmission of light along a plastic rod, a plastic nasolacrimal probe was devised and constructed to fit an external light source

(Fig. 1). Material is now available that makes possible the construction of such probes, which are comparable to the Bowman probe No. 3 (less than 1 mm. in diameter). This plastic probe is more easily inserted than a metal one of equivalent size. The light source may be a small flashlight transilluminator or any other easily portable apparatus. Instruments which emit parallel rays of light will produce greater light intensity at the end of the probe and are generally more satisfactory. When the probe is fully inserted into the nasolacrimal sac against the surface of the nasal bone (Fig. 2), the light is readily seen in the nasal cavity. The point of transillumination marks the site for incision and entrance into the nasolacrimal fossa (Fig. 3). This site can then be marked with a dye, or, better, the operation can be started with the probe in position and whenever necessary the light can be turned on for reorientation. After an opening has been made in the bony wall, the sac is easily identified by again using the lighted probe, and excision of a part of the wall can be done in the usual manner. In other respects this procedure does not differ from those previously described, but it does offer an accurate and easy means of orientation for those generally unfamiliar with the landmarks of the nasal cavity.

Mr. Bernard A. Maloney, of Portland, Ore., constructed the instrument, and Dr. Thomas Talbot made the drawing.

A GONIOSCOPIC STUDY OF FISTULIZING OPERATIONS

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NEW YORK

THE MECHANISM by which surgical procedures control glaucoma is not known, a fact which is not remarkable since the cause of the disease itself is not known. The present study is an attempt to demonstrate whether gonioscopy can shed light upon this point. Examination was made with the Koeppe lens and binocular gonioscope or with the Allen Gonioprism and slit lamp, the patients being unselected except for their having had fistulizing antiglaucoma operations. After the records with insufficient data or length of follow-up study had been discarded, there remained 91 eyes for analysis, all of which I had personally examined. None was followed for less than six months. All but 7 were followed over one year—48 from one to three years, 17 from three to five years, and 19 over five years.

The generally accepted mode of action of fistulizing operations may best be described by quoting Duke-Elder.[1]

> In all these operations the object is to create a fistulizing scar which will remain a permanently open channel for drainage from the anterior chamber to the subconjunctival space [Fig. 1]. The perfect trephine scar is filled with delicate connective tissue derived from the subconjunctival tissue, full of empty spaces intercommunicating and traversing its extent, and free from endothelium. Closure may follow from dense scar tissue derived from a raggedly cut wall in the sclera, or from the growth of endothelium into the area, or from prolapse of the ciliary processes. The most permanent and efficient factor in keeping a patent channel would appear to be the migration of the pigmentary cells of the iris, which, being ectodermal, are not engulfed in mesodermal overgrowth; for this reason it is to be expected that the filtering scar of an iris inclusion operation has more chances of survival than that of a sclerectomy.

At this time I am not concerned with other, nonfistulizing operations, with the possible exception of the iridectomy in cases of acute glaucoma. Von Graefe originally suggested that with this procedure removal of part of the iris diminished secretion of aqueous humor. Since that time numerous theories have been advanced, the most favored being that of Weber and Collins, who stated that mechanical removal of the iris before permanent adhesions had been established permitted drainage of fluid through the normal exposed trabeculum and Schlemm's canal. Failure to effect such exposure of the trabeculum is thought to result in failure of the operation. Other persons have believed that (1) the cut, noncicatrizing iris

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Presented at the Eighty-Sixth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., May 31, 1950. (Tr. Am. Ophth. Soc. 48:118-127, 1951.)

From the Institute of Ophthalmology of Presbyterian Hospital, and the Department of Ophthalmology of Columbia University College of Physicians and Surgeons.

1. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, Vol. 3, p. 3405.

border presents a new absorptive surface, (2) a filtering scar may be formed, and (3) vasomotor reflex arcs are cut. The average incidence of success of this procedure in the hands of many operators has been summarized by Duke-Elder as about 60%. It is also interesting to note from the same source that figures compiled in 1908, when no other procedures were in popular use for glaucoma of any type, indicated success in 80% of all cases of acute congestive glaucoma, in 53% of cases of chronic congestive glaucoma, and in 33% of cases of chronic noncongestive glaucoma.

Although most reports [2] concerning antiglaucoma operations emphasize the importance of fistulization as a permanent accomplishment, my own observations lead me to question this concept.

It does not seem reasonable that a mechanism as delicately balanced as that regulating intraocular pressure can be permanently rectified by such a gross and mutilating procedure as the usual filtration operation, particularly since such an operation can rarely be done in exactly the same way on repeated occasions and since there is no way of graduating the amount of drainage which may occur. Sporadically dissenting voices have been raised. More doubt about these fistuliz-

Fig. 1.—Diagram of classic fistulization theory.

ing procedures has appeared in the foreign literature than from the English-speaking countries.[3] No one professes sufficient knowledge to explain in detail just how such

2. Kronfeld, P. C., and McGarry, H. I.: Results of Surgical Treatment of Acute Congestive Glaucoma, Quart. Bull. Northwestern Univ. M. School, **18**:203-214, 1944. Sugar, H. S.: The Practical Applications of Gonioscopy to Glaucoma Surgery, Am. J. Ophth. **25**:663-671, 1942. McLean, J. M.: Gonioscopy in Relation to Common Glaucoma Operations, Tr. Am. Acad. Ophth. **45**:176-183, 1941. Troncoso, M. U.: Use of Tantalum Implants for Inducing a Permanent Hypotony in Rabbits' Eyes, Am. J. Ophth. **32**:499-508, 1949. Bick, M. W., and Haines, R. W.: Local Use of Heparin in the Eye: Pellet Implantation at an Experimental Filtering Site, ibid. **32**:774-780, 1949.

3. François, J.: La gonioscopie, Louvain, R. Fonteyn, 1948. Amat, M. M.: The Mechanism of Action of Antiglaucomatous Operations, Arch. Soc. oftal. hispano-am. **6**:1169-1181, 1946; abstracted, Am. J. Ophth. **30**:656, 1947. Busacca, A.: Éléments de gonioscopie normale, pathologique et expérimentale, São Paulo, Rossolillo, 1945. Weekers, L.: Mode d'action des operations antiglaucomateuses, Ophthalmologica **118**:564-574, 1949. di Luca, G.: Biomicroscopic Examination of Cicatrices of Antiglaucomatous Operations, Rass. ital. ottal. **17**:304-317, 1948; abstracted, Am. J. Ophth. **32**:750, 1949. Duke-Elder, W. S.: The Physiology of the Intraocular Fluids and Its Clinical Significance, Tr. Am. Acad. Ophth. **54**:18-25, 1949.

operations attain their end. Of necessity, because of our superficial knowledge concerning intraocular physiology, only general explanations can be offered, such as those suggesting interruption of a neurovascular crisis or an alteration in the amount of interstitial tissue fluid.

Animal experimental work has been inconclusive in the sense that filtering scars have not developed in the cat or rabbit. Ellett [4] noted that the wounds filled in with tissue practically identical with the surrounding sclera. The conclusion usually drawn from such work has been not that true filtration is rarely established but that animals are not suitable for such experimentation. There have been several reports [5] of human eyes removed after successful operations for glaucoma, but the evidence in these, again, is not conclusive. In some reports the period following operation was short; in others the clinical description was scanty, and in still others the eyes were of the filtering bleb type with grossly patent openings, in which filtration admittedly occurs.

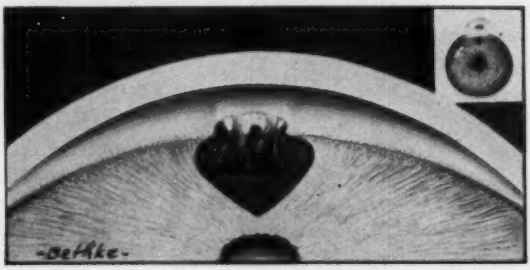

Fig. 2.—Gonioscopic and external appearance of fistulizing trephine operation.

As the result of gonioscopic and slit-lamp examinations of 91 eyes in this study, four categories were established:

1. Eyes which gave evidence gonioscopically of an internal fistula and which also appeared to be filtering externally, as shown by a conjunctival bleb or pitting edema of the conjunctiva or both (Fig. 2).

2. Eyes which gonioscopically appeared to have an internal opening but which on external examination revealed no bleb and no evidence of conjunctival edema.

3. Eyes in which no evidence of an internal dehiscence could be observed gonioscopically but which had the external characteristics of filtration.

4. Eyes in which there was no evidence, either externally or internally, of fistulization.

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4. Ellett, E. C.: A Study of the Healing of Trephine Wounds of the Sclera and Corneoscleral Junction, Tr. Sect. Ophth. A. M. A., 1914, pp. 390-394.

5. Elliot, R. H.: The Histology of the Trephine Disc in Glaucoma Operations, Tr. Ophth. Soc. U. Kingdom **38**:227-249, 1918. Verhoeff, F. H.: Histological Findings After Successful Sclerostomy, Arch. Ophth. **44**:129-138, 1915. Holth, S.: Anatomical Examination of Six New Cases of Subconjunctival Fistula Scars from Five Months to Six Years After Successful Iridencleisis or Limbal Sclerectomies in Chronic Glaucoma, Brit. J. Ophth. **6**:10-22, 1922. Greeves, R. A.: Some Observations of Four Trephined Eyes Examined Microscopically, Tr. Ophth. Soc. U. Kingdom **36**:445-451, 1916.

Usually it was relatively easy to make such distinctions. In order that the error might be in the direction of the more generally accepted filtration theory, eyes with large firm blebs were considered as showing external evidence of filtration, even though their character, firmness, and absence of pitting edema raised serious doubt as to whether they should be so classified.

Twenty-six eyes (28%), including 20 with trephinations, five with iridencleises, and 1 with sclerectomy with iridectomy, appeared in the first group. Of these, 15 (58%), all with trephinations, were grossly hypotonic. In none was the intraocular pressure above normal. Interestingly, prolonged hypotony was not necessarily disastrous to the eye, one patient having been followed uneventfully for four and one-half years with a tonometric reading of about 7 mm. Hg. Of these 15 eyes, seven suffered no loss of vision or field during periods of one to four and one-half years.

There can be no doubt that true filtration of aqueous through an opening in the sclera to the subconjunctival space can occur. Usually a large bleb is present,

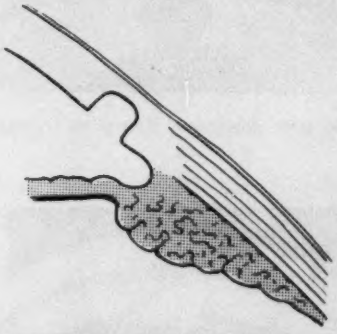

Fig. 3.—Diagram of nonfistulizing trephine area, which would appear patent gonioscopically.

which, when pressed with a glass rod, readily presents pitting edema. At times demonstrable edema is present subconjunctivally over the upper half of the globe. But, as has been noted, such eyes are frequently hypotonic. It is theoretically possible surgically to produce the exact amount of filtration necessary to maintain the pressure of the eyeball at the correct physiological level, but the surgeon actually has little control over this. In the trephining procedure rarely is other than the 2.0 or the 1.5 mm. instrument used. In iris inclusion operations little attempt is made to relate the length of the incision to the level of the intraocular pressure. Not all the eyes in the first group showed pitting edema, some having had rather firm blebs, so that even in this group it is questionable whether real fistulization occurred in all cases.

The second group, which showed an internal opening gonioscopically but not externally, comprised 15 eyes (17%). In seven of these the intraocular pressure was controlled, and in eight it was uncontrolled. There were no eyes with hypotony. The presence of true fistulization in this group must be considered equivocal, since it is quite possible to have a large opening apparent gonioscopically but yet have its base solidly and effectively filled with impermeable scar tissue (Fig. 3).

Seven eyes (8%) showed an external bleb but no visible internal opening (Fig. 4). In all the eyes the tension was controlled. One, on which an iridencleisis had been done, showed pitting edema and can be considered as presenting true fistulization.

The remaining 43 eyes (47%) showed no demonstrable evidence of fistulization either externally or internally (Fig. 5); yet in 31, or 72%, the intraocular pressure was controlled. No case of hypotony was encountered. Most observers have assumed that the absence of an observable gonioscopic dehiscence does not preclude the possibility of microscopic or macroscopic openings being present in the retro-

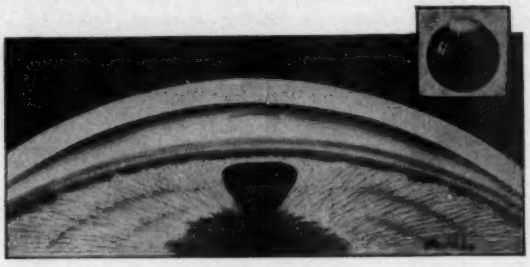

Fig. 4.—Gonioscopic and gross appearance of trephine opening which has become filled with connective tissue.

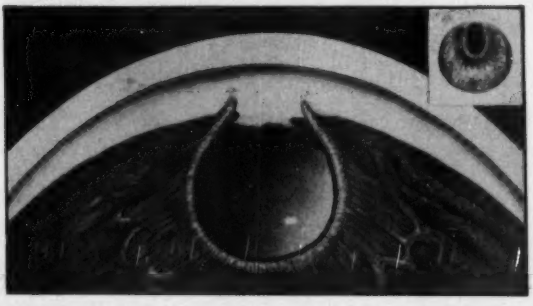

Fig. 5.—Gonioscopic and external appearance of iridencleisis, which shows no evidence of fistulization.

iridal, or unobservable, portion of the wound. This possibility, although it has not been proved microscopically, cannot be denied and would explain the one case noted above in which no internal opening could be seen and yet conjunctival edema was present. All gonioscopic observation points to the formation of firm connective tissue adhesions between the iris and the scleral wall, such as occur regularly when the iris and the scleral wall are in contact for any extended period. The prolapse of the iris which occurs as a postoperative complication of cataract extraction does not show such microscopic openings; yet this is fundamentally similar to an iris inclusion procedure. Busacca's belief that cysts form subconjunctivally and that

these cysts fill with aqueous, which is drained by lymphatics taking origin in the walls of the cyst and discharging into the bulbar conjunctival network, has not been demonstrated histologically.

It is likely that the 15 cases in group 2 should functionally be included in group 4 and that even this figure of 64% of the eyes not demonstrating actual filtration after operation is an underestimation.

COMMENT

Since it is possible that two-thirds of the eyes examined do not represent true filtration and since about two-thirds of the eyes without obvious filtration have controlled intraocular pressure, what, then, is the means by which such control is attained? At present, this question is unanswerable except in the most general terms. It may be that such action is similar to that of the iridectomy in cases of acute glaucoma. It is reasonable to suppose that an eye which has had elevated pressure for a long period will require longer to adjust its neurovascular system after operation than would one in which the condition had been present for only a matter of hours. The longer period of drainage before healing in the average fistulizing operation could supply the time required for such readjustment.

CONCLUSIONS

Ninety-one eyes undergoing filtering operations for glaucoma were examined gonioscopically.

1. Of these, about two-thirds did not show gross evidence of filtration.

2. Of the remaining one-third, which could be considered to show filtration, about one-half were grossly hypotonic.

3. About two-thirds of the eyes without obvious filtration nevertheless had controlled pressure.

4. Exclusive of the hypotonic eyes, the pressure was controlled in 73%.

It is believed that in most cases of glaucoma success in fistulizing operations is due not to mechanical fistulization but, more probably, to trauma of the uveal tract and readjustment of the neurovascular system.

UVEITIS, POLIOSIS, AND ALOPECIA IN SIBLINGS

A Case Report

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AND
WILLIAM L. BENEDICT, M.D.
ROCHESTER, MINN.

REPORTS on the incidence of the syndrome of uveitis associated with poliosis, alopecia, dysacousia, and vitiligo include only one instance of the disease in two members of the same family. Salus,[1] in 1932, reported the occurrence of Harada's disease two months apart in sisters. A report of two additional typical cases is submitted because of their close occurrence in one family.

In this instance a girl, aged 17, first demonstrated signs of uveitis in February, 1944. Two months later, in April, her next older brother, aged 19, showed a similar condition. The courses of the disease in these siblings were similar in all respects. In neither case did deafness or vitiligo appear.

CASE 1.—A girl of Serbian parents, at the age of 17, in the first week of February, 1944, had in both eyes what was first thought to be conjunctivitis. She complained of a foreign body sensation, "as if sand were in the eyes." Several weeks later she was found to have severe plastic iritis with pronounced clouding of the vitreous and limitation of vision to perception of hand movements. A thorough physical examination revealed no systemic disease; the Mantoux and Wassermann tests gave negative results. Tonsillectomy was done, and she was given six injections of typhoid and paratyphoid vaccine, together with sulfonamides and various eye drops. In the first part of May, 1944, a transfixion of the iris of the left eye was performed. In May, also, she began to lose a considerable quantity of hair, so that she became almost completely bald except for a fringe of hair around the edges of the scalp. The eyebrows became thin. In November, 1944, the hair began to grow back but came in white instead of black, the normal color of her hair. During the same period of new growth, the eyelashes turned white and have remained so until the time of this report. By August, 1946, the caput hair had become almost completely black except for a few "gray" hairs. The patient and her sister state that at no time did she ever have any hearing difficulty or vitiligo. However, "the skin on the face broke out at the beginning of the illness," and this condition has persisted, with several recurrences and exacerbations which have been assigned to manifestations of contact dermatitis.

The patient was first seen at the Mayo Clinic on May 23, 1944. At this time vision in each eye was limited to light perception with good, full light projection. Extraocular movements were normal; tactile tension was —2 in each eye, and there was conjunctival hyperemia Grade 1 to 2. With the slit lamp one could see a few small keratic precipitates with many cells floating in the aqueous. There was a complete posterior synechia in each eye. The irides were thickened and edematous, and the iridic vessels were dilated.

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1. Salus, R.: Harada'sche Krankheit, Klin. Monatsbl. Augenh. **89**:84-87, 1932.

The results of general physical examination were essentially normal. The blood pressure was 110 mm. Hg systolic and 70 diastolic; the pulse rate, 84; the temperature, 98.6 F. The urine was normal, and initial and subsequent blood cell counts and smears always remained within normal limits. An agglutination test for brucellosis gave a negative result. The patient had a negative serologic reaction for syphilis and a normal thoracic roentgenogram. Cultures of vaginal secretion yielded no pathogens. She had a few carious teeth.

From May 30 to Oct. 20, 1944, she received gold sodium thiosulfate, 25 mg. every two days for a total dose of 1,790 mg., with some diminishing redness of the eyes. By November, 1944, the irides were atrophic and the lenses cataractous, though she maintained light perception.

In Jan., 1945, sensitivity to atropine developed, disappearing after discontinuation of the drug. Gold therapy was resumed on Feb. 15, 1945, and was continued until April 28, 1945, with a total dose of 500 mg., but no noticeable change occurred in the eyes.

On July 17, 1950, a linear cataract extraction was done on the right eye. She again exhibited sensitivity to atropine and, later, to scopolamine; this cleared with use of a 2% tripelennamine ("pyribenzamine") hydrochloride cream. A pupillary opening was not obtained by operation, and there was no improvement.

On Nov. 9, 1950, iridotomy was done on the right eye for occluded pupil, with, again, a severe cutaneous reaction, not due to atropine, after operation. Cortisone, 100 mg. a day, was administered intramuscularly, but the pupil had closed over by the seventh postoperative day and there were many wrinkles in Descemets' and Bowman's membranes. No benefit was obtained from this operation.

On Feb. 14, 1951, a needling operation was done on the right eye, with no subsequent satisfactory opening. Since then the right eye has remained soft and phthisical, and at last examination, in June, 1951, it was deviating laterally.

On Feb. 26, 1951, linear extraction of a mature cataract was done on the left eye. After this there was again a severe cutaneous reaction, the cause of which is unknown. Cortisone drops, 1%, were administered every two hours, with some whitening of the globe, and by June, 1951, vision had improved slightly to ability to count fingers. On June 18 a needling of the left eye was done, with no beneficial results, and on June 21 an iridocapsulectomy was performed. After this the eye became phthisical, with reduction in light projection.

Case 2.—The next older brother, aged 19, had been living at home with the family since January, 1944. He had been working and was not in any close contact with his sister. His illness began in the latter part of April, 1944 (about two months after the onset of his sister's illness), with redness of the eyes, followed by progressive loss of vision and photophobia. His local physician found septic tonsils Grade 4, and these were removed on May 9. His Mantoux reaction was negative, but he had several infected teeth. He had had one injection of typhoid and paratyphoid vaccine, with no ocular benefit.

He was first seen in the Mayo Clinic on May 23, 1944, at which time vision was 5/60 in each eye, with full visual fields, normal extraocular movements, and a negative tactile tension. The conjunctivas were slightly injected, and there were a few small keratic precipitates and many cells floating in the aqueous. There were many fine posterior synechias, and the irides were thickened. The results of general physical examination and laboratory tests were essentially normal. Blood cell counts and smears were normal, and serologic reactions of the blood were negative; the reaction to purified protein derivative of tuberculin (first strength) and agglutination reactions for Brucella were negative. A thoracic roentgenogram was normal. There were several carious teeth.

About the first part of June, 1944, he began to lose the caput hair, but never to the extent of getting bald spots. In November regrowth of hair began, but the new hair came in white instead of the original black color. About this time his eyelashes turned white. At no time did he have any hearing difficulty or vitiligo.

From May 30 to June 5, 1944, he had four intravenous injections of typhoid vaccine and one session in the fever cabinet, with no improvement. From June 15 to Aug. 9 he received a total of 1,635 mg. of gold sodium thiosulfate, and from Jan. 27 to May 30, 1945, he received 1,145 mg. of the gold compound, with no ill effects and only subjective improvement in the eyes and vision.

By January, 1945, the irides were atrophic and cataracts had developed. In March, 1945, the eyes had whitened considerably, but there were many keratic precipitates; by November, 1945, the corneas were clear and the anterior chambers shallow. The lenses were completely cataractous, and the eyelashes were almost all white.

On Nov. 19, 1945, a linear cataract extraction was done on the left eye. A small pupillary opening was obtained, which lasted only a short while before closing over again. On Aug. 6, 1946, vision in each eye was equal to light perception with good light projection. The lashes in the right eyelids were all black again, but those in the left lids were nearly all white. The caput hair was normal. Tactile tension was normal, but the irides were atrophic.

On July 15, 1947, vision was limited to perception of hand movements in each eye, and tension was 15 and 19 mm. Hg in the right and left eyes, respectively. The right eye showed a calcareous lens, atrophic iris, and shallow chambers. In the left eye the cornea was normal; the anterior chamber was of normal depth, but the surgical coloboma was closed.

On July 5, 1949, a Wheeler iridotomy was done on the left eye, but the opening immediately filled with blood. On July 13, 1950, there was demonstrated a small pupillary opening in the left iris, the right eye remaining unchanged. Refraction of the left eye revealed vision of 6/7 with a +8.50 D. lens, and with +3.00 D. added vision for near equaled 14/21.

On July 17, 1950, a linear cataract extraction was done on the right eye, and two weeks later a faint red reflex could be obtained with the ophthalmoscope. On Nov. 8 it was found that the pupillary opening previously made in the right eye had closed, and on the following day an iridotomy was done. This resulted in a fairly good pupillary opening, although the fundus could not be seen with the ophthalmoscope. While in the hospital, the patient received 100 mg. of cortisone a day.

When the patient was last seen, on Feb. 16, 1951, corrected vision was as follows:

R. E.: +9.00 D. sph.; V = 6/15
L. E.: +8.50 D. sph.; V = 6/6

The eyes were quiet, and no further changes are anticipated.

In this family there were eight children, three of whom were not living at home at the time these two siblings manifested the disease. The mother and the other three children have not shown any similar disease. The father died when these patients were small.

It is interesting to note that the time interval between the onset of the disease in these two patients, as well as that of the disease in the case reported by Salus, was two months. Although the Vogt-Koyanagi syndrome and Harada's disease are now thought to be variants of essentially the same disease, Salus made the diagnosis of the latter disease in his cases, whereas the present two cases fall into the former group.

METHODS FOR THE EARLY DIAGNOSIS OF MULTIPLE SCLEROSIS

Observations with Special Reference to the So-Called Ocular Type

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IN ORDER to establish the diagnosis of multiple sclerosis, certain basic facts must be borne in mind:

1. Multiple sclerosis is characterized by the scattered occurrence of demyelinated patches in the white matter throughout the central nervous system. These patches, or plaques, develop in a characteristic way. The myelin sheaths are the first structures involved; they are followed by lymphocyte and plasma cell infiltration, by microglial and astrocytic proliferation, fat-granule-cell response, and connective tissue reactions.[1] Axis-cylinders are damaged to a less degree; sometimes they are naked but not injured at all. The ganglion cells, even in areas with active degeneration, show no impairment. However, the spinal nerve roots are sometimes affected.

2. The plaques include sensory and motor pathways.

3. The neurological symptoms vary greatly, according to the location of the lesions within the central nervous system. Clinically, certain types of the disease may be distinguished, such as the ocular and the spastic type. Their relative frequency of occurrence has been tabulated by Wilson [2] and, more recently, by Carter, Sciarra, and Merritt.[3] The objective symptoms which are found most frequently are ocular or motor. According to Wilson, motor symptoms, including weakness, ataxia, and tremor, are present in 56.5% of cases (other authors give values up to 80%); ocular symptoms occur in 14.3% (up to 40% in other statistics). These ocular disturbances include retrobulbar neuritis with subsequent atrophic changes in the nerve head, diplopia, horizontal or vertical nystagmus, and pupillary changes.

While it is the generally accepted opinion that pupillary disturbances are rather infrequent in multiple sclerosis, I found that they are almost always present in advanced cases, and very often in early cases.

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1. Zimmerman, H. M., and Netsky, M.: Pathology of Multiple Sclerosis, A. Res. Nerv. & Ment. Dis., Proc. **28**:271-312, 1950.

2. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, Vol. 1, pp. 156-160.

3. Carter, S.; Sciarra, D., and Merritt, H. H.: The Course of Multiple Sclerosis as Determined by Autopsy Proven Cases, A. Res. Nerv. & Ment. Dis., Proc. **28**:471-511, 1950.

The pathological process itself, i. e., demyelination, is nonspecific. The characteristic of multiple sclerosis is the multiplicity of lesions, and no diagnosis is well established unless the presence of at least two, and possibly more, sites of lesions is proved. For instance, absence of abdominal reflexes in connection with the Babinski sign, or even with a hemiplegia, cannot be considered to be caused by multiple lesions, since these signs may be due to one lesion in the pyramidal tract. Similarly, retrobulbar neuritis may produce a number of clinical symptoms, such as blurred vision or pain on moving the eye, but this is not necessarily due to multiple lesions; however, the diagnosis of multiple lesions would be established in a case in which retrobulbar neuritis is combined with hemiplegia.

It is not at all necessary for the diagnosis that the symptoms due to demyelinating lesions be situated far apart; it is essential only that they are located in different neurons, and that they are not caused by a single, though extensive, process, such as an inflammation or tumor.

The lesions may occur in different neurons with symptoms within the same organ—for instance, when ocular symptoms include those of retrobulbar neuritis and impairment of intraocular or extraocular muscle function.

The possibility of syphilis of the central nervous system, which may imitate any syndrome due to multiple sclerosis, must be eliminated.

It is characteristic of the course of multiple sclerosis that it occurs in sudden attacks, which appear without prodromes. These acute exacerbations are often followed by intervals of more or less complete remission.

Initial symptoms are frequently very slight, abortive, or even latent; the classic description that multiple sclerosis in its early stages does *multa, non multum* is correct in the majority of cases. The more recurrences take place, the more permanent and severe symptoms remain, although cases not infrequently exist in which the first attack of the disease produces severe permanent symptoms. In more benign cases the first attack, or attacks, may be mild, characterized only by subjective symptoms, and may go unnoticed. They may be followed by a remission, in which all symptoms disappear, clinically at least. This so-called symptomless interval between attacks may be of shorter or longer duration, sometimes lasting many years, or even the rest of the patient's lifetime.

Since it is important to discover the early, minute, or latent symptoms, and thereby demonstrate the presence of multiple lesions, special methods of investigation may be needed. Only such methods as proved valuable during many years of my experience but are not described in the literature in connection with the early diagnosis of multiple sclerosis will be discussed in this article.

An attempt will be made to answer the question of how a diagnosis can be established (1) when ocular symptoms due only to one lesion point to the possibility of multiple sclerosis and the usual neurological methods yield no results, or (2) when neurological symptoms outside the visual apparatus, due only to one lesion, raise the suspicion of multiple sclerosis, and the usual ophthalmologic methods (examination of fundus, visual fields, and extraocular muscles) yield no results.

For a description of the generally known methods, the reader is referred to the comprehensive article on the subject by Schumacher.[4]

4. Schumacher, G. A.: Multiple Sclerosis, J. A. M. A. **143**:1059-1065 (July 22); 1146-1154 (July 29); Treatment of Multiple Sclerosis, ibid. **143**:1241-1250 (Aug. 5) 1950.

I. DETECTION OF LATENT MOTOR SYMPTOMS OUTSIDE THE VISUAL APPARATUS

In cases in which a single ocular sign, such as retrobulbar neuritis or transitory diplopia, indicates the possibility of multiple sclerosis but ophthalmologic examination shows no other abnormality, an attempt should be made to find additional signs of lesions outside the visual apparatus.

Symptoms which are most easily discovered preclinically are those concerned with the motor functions—paresis, tremor, or disturbances of the equilibrium in the widest sense of the word.

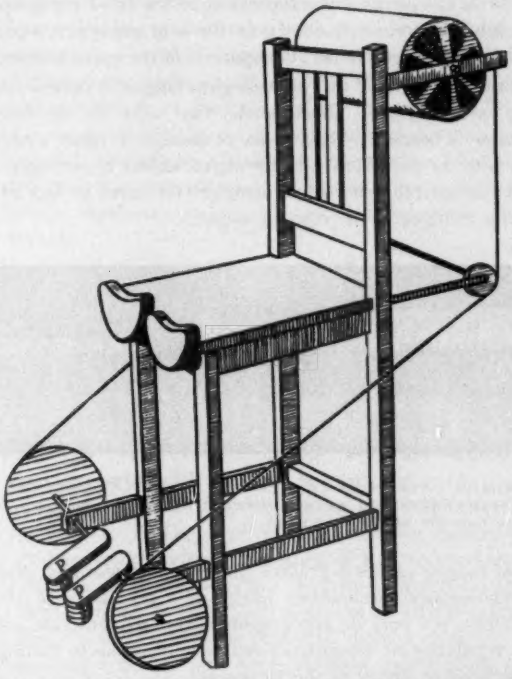

Fig. 1.—Foot ergograph. The patient sits on a chair, with knees supported by knee rests, and feet attached to weighted pedals (*P*). Motions of the feet (lifting and lowering of the weights) are transmitted to a kymograph recorder.

A. Ergographic Methods.—Testing of rough strength is usually done by comparing the intensity of grip of the right and the left hand or by estimating the resistance the patient is able to offer to passive movements in the different joints. These methods are crude and cannot demonstrate finer differences. For greater precision, dynamometers are widely used. The maximum pressure of the grip exerted by each hand is measured, once or repeatedly. This method is limited to the hands, in particular to the fingers, and does not test movements in other joints. The same is true of Mosso's ergograph, in which a weight is lifted repeatedly at regular intervals with either a finger or a hand, and the resulting curves are

recorded, yielding comparable values for the right and the left side. The ergographic curves reveal asymmetrically increased fatigue in cases of unilateral latent or slight paresis.

In view of the pronounced unilaterality of the upper extremities in normal man, results can be considered unequivocal only if the right hand fatigues earlier than the left in right-handed patients or if the left hand tires sooner than the right in left-handed persons.

Right- or left-footedness also exists in man, but it is less pronounced.[5] Therefore, the foot ergograph (Fig. 1) yields more indicative symptoms than does the hand ergograph. It is a necessary complement to the hand ergograph, since latent paresis of the lower extremities, shown in the foot ergogram, occurs at least as frequently, and perhaps even oftener, than paresis of the upper extremities (Fig. 2).

It has recently been shown [6] that physiological fatigue in normal man is of central nervous origin, symmetrically affecting the two sides of the body. Therefore, asymmetric fatigue is necessarily expressive of damage to either a nervous center or its connections with the peripheral effector organ, unless hypertrophy (for instance, that produced by unilateral exercise) or atrophy (produced by lack of exercise) had created unilateral changes in the effector organ.

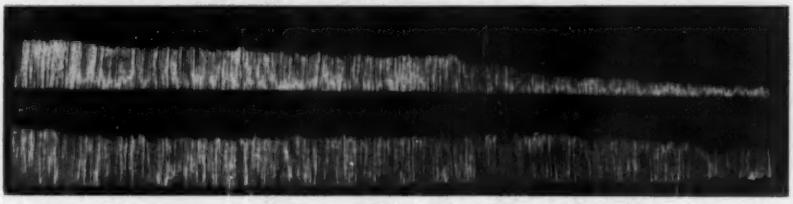

Fig. 2.—Ergographic curves of the right (*A*) and the left (*B*) foot. The two sides show equal excursions in the beginning; i. e., rough strength is equal on the two sides, but the right side fatigues sooner than the left (latent paresis).

Physiological fatigue causes a gradual decrement of working capacity, whereas interfering psychosensory mechanisms modify the regularity of the decrease in function. Therefore, not only do ergographic curves demonstrate unilateral weakness, but their regularity or irregularity makes it possible to distinguish between organic and psychogenic origin of the weakness.

B. "Retention-of-Position" Curve.—Patients with a slight or latent paresis of an upper or a lower extremity are not able to retain the position of the elevated limb on the weakened side as long as on the normal side. To obtain the "retention-of-position" curve, the patient, who is lying on his back, is asked to lift both upper and/or both lower extremities at an angle of about 45 degrees. He is instructed to hold this posture as long as possible, to allow arms and/or legs to fall only when it becomes impossible to maintain their position, and to resist as much as he is able

5. Schemann, H.: Ergographische Studien an Gesunden und Hirnverletzten nach der fussergographischen Methode O. Lowenstein's, Inaugural Dissertation, Bonn University, 1933.

6. Lowenstein, O., and Loewenfeld, I. E.: Disintegration of Central Autonomic Regulation During Fatigue, J. Nerv. & Ment. Dis., to be published.

the gradual descent of the extremities as they fatigue. If one side is lowered faster than the other side, increased fatigability of that side, i. e., unilateral weakness, is shown.

In order to make the method as objective as possible, the position curve of each limb is recorded individually on a kymograph, and the results are then compared. The purpose of individual recording is to eliminate any suggestion offered by increased fatigability of one weakened arm or leg which may cause the patient to lower all extremities simultaneously. On the other hand, successive testing of the various extremities may be a source of error; in view of the central nervous factor in all fatigue processes, the preceding examination of the right arm or leg may leave remnants of fatigue (*Ermüdungstrückstand*), which add to the fatigue of the later-examined left extremities. To avoid this error, intervals of rest must be interposed between the individual examinations, and the tests must be repeated several times in different sequence. This can be done easily, since the procedure is very simple.

This method permits elimination of the influence of psychogenic mechanisms more effectively than is possible in ergographic experiments. Unilateral shakiness may develop; whether it is organic or psychogenic can be distinguished by its regularity or lack of regularity and by its modifications under the influence of psychosensory stimuli.

C. Registration of the Deep Reflexes.—Several methods are known for recording the deep reflexes, particularly the ankle and patellar reflex. Unlike an earlier technique,[7] in which the patient is sitting, I record the reflexes of the patient when he is lying on his back, and therefore more relaxed, allowing the reflexes to be elicited more readily. In order to improve the relaxation of the lower extremities further, knee supports, which can be raised or lowered, are placed in the popliteal fossae. When the patellar reflexes are examined, elastic rubber bands are placed under the patient's heels. They allow oscillations, which are recorded; in this way, the reflexes of the right and the left side may be compared.

In spite of all precautions for relaxing the muscles, subjective factors remain and cannot be eliminated: 1. The patellar tendon may be situated deeper on one side than on the other, and therefore stimulation of the receptors may be different in spite of equal stimuli. 2. It is natural that the patient directs his attention toward the extremity which is being tested. Such direction of attention toward any part of the body modifies the muscle tonus of that part, thereby changing the course and extent of the resulting reflexes. For these reasons, this method should be used with caution.

D. Recording of Muscle Tonus.—The same source of error exists in all methods for measuring muscle tonus in which the patient's attention is focused on the part of the body undergoing examination. Wartenberg [8] recently described the usefulness of a simple experiment called the "pendulousness test." The patient sits on the edge of a table, with his legs hanging freely. The examiner first lifts the patient's legs simultaneously to the same horizontal level and then releases them, allowing them to swing freely. Of course, tonus differences in the two legs cause inequalities in

7. Sommer, R.: Psychopathologische Untersuchungsmethoden, Leipzig, Wilhelm Engelmann, 1929.

8. Wartenberg, R.: Pendulousness of the Legs as a Diagnostic Test, Neurology **1**:18-24, 1951.

swinging time and quality. For more exact evaluation, the movements may easily be recorded by inked brushes fixed to the feet, which mark the movements on a piece of paper beneath. This test is excellent by virtue of both simplicity and precision, but it can be applied only to patients who are able to relax sufficiently to allow correct performance of the examination. However, it is sometimes impossible to make the patient relaxed enough, particularly when he is afraid and tense.

Therefore, muscle tonus can best be tested by techniques which do not require the patient to relax voluntarily, and which avoid involving him in a vicious circle by directing his attention toward that part of the body from which attention should be removed.

For many years, I have been using a method for measuring the muscle tonus which has become known as the "tonus reflex method," or, when used for other purposes, "method of unconscious-expression movements."[9]

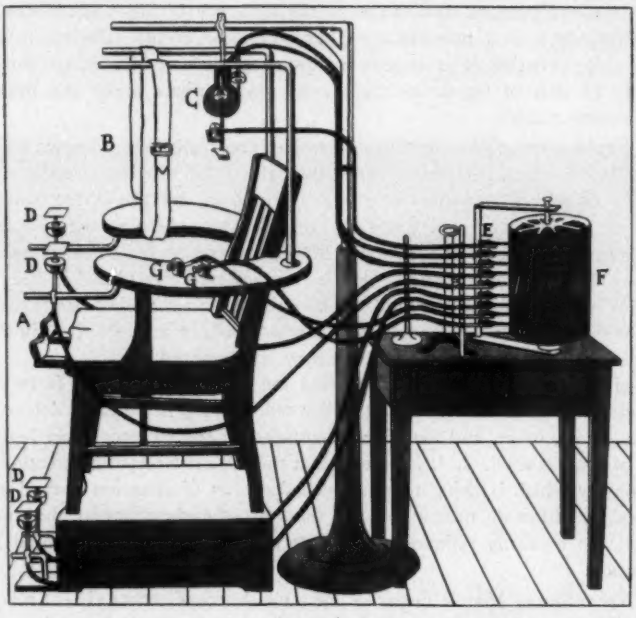

Fig. 3.—Apparatus for recording involuntary muscle tonus.

The recorded movements are below the threshold of perceptivity. The patient sits on a chair (Fig. 3), and he should be comfortable in order that relaxation may be possible. Knee supports (*A*) are placed in the popliteal fossae, beneath the popliteal arteries; the arms are symmetrically suspended in slings (*B*), in slight abduction, so that their weight rests on the brachial arteries. The head is connected with an apparatus (*C*) which mechanically analyzes its movements into their (*a*) forward and backward, (*b*) lateral, and (*c*) rotation components. The palms of the hands and the soles of the feet are connected with pneumatic capsules (*D*) that transfer pressure exerted on them to small Marey capsules (*E*), by which the movements are recorded on a kymo-

9. Lowenstein, O.: Experimentelle Hysterielehre, Bonn, Friedrich Cohen, 1923, p. 11.

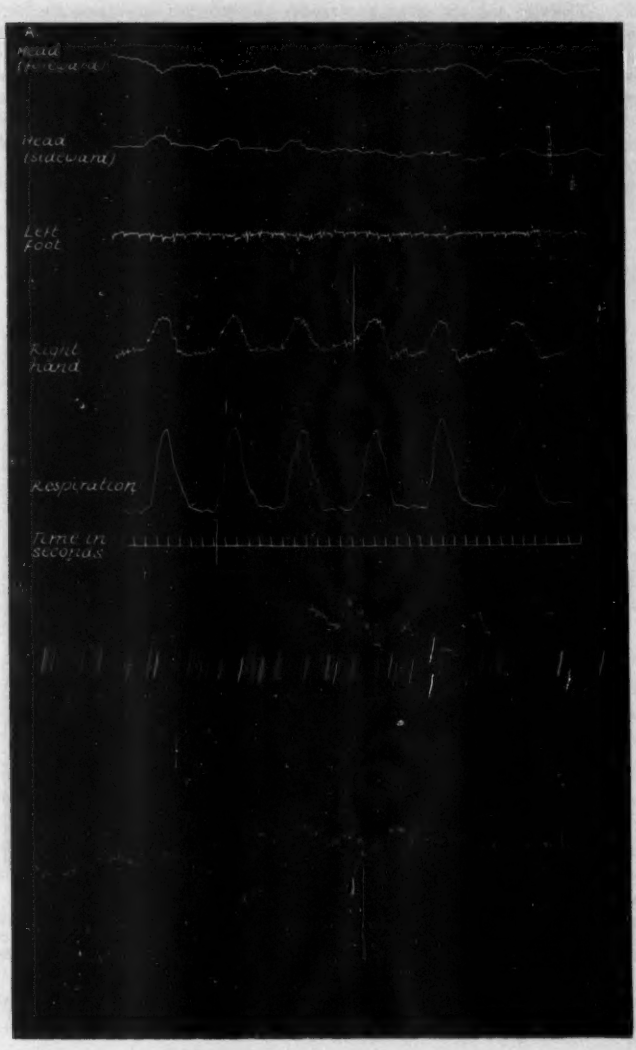

Fig. 4.—Normal (*A*) and abnormal (*B*) muscle tonus curves.

(*A*) The curves are composed of larger oscillations (respiration), small regular oscillations (pulse), and irregular fast autochthonous motions.

(*B*) A verbal stimulus (at +) elicits a tonus reflex which is more pronounced on the right than on the left side and causes a tremor in the right hand which is similar to, though slightly, less marked than, that which was previously seen in the left hand only.

graph (*F*). Thoracic and abdominal respirations are recorded simultaneously by means of pneumatic capsules (*G*) fastened to the chest and the abdomen. The patient has nothing to do but sit and look at a point at eye level on the opposite wall.

The motion curves of the head and extremities consist of large oscillations, due to respiration, with superimposed (*a*) fine, regular oscillations of the pulse and (*b*) irregular, autochthonous oscillations (Fig. 4). As soon as the muscle tonus in any part of the body is modified, the degree to which pulse, respiration, and autochthonous oscillations appear is also modified. In this way, the curves furnish a sensitive record of the changing tonus.

Any change in the contents of consciousness—for example, each word that is heard, or each sensation perceived—alters the tonus of the entire muscular system of the body. These modifications in tonus become even more pronounced by the application of psychological or sensory stimuli.

By this method, very fine tonus differences, due to latent or slight paresis, can be revealed. Normally, tonus modifications caused by psychosensory stimuli spread symmetrically over the

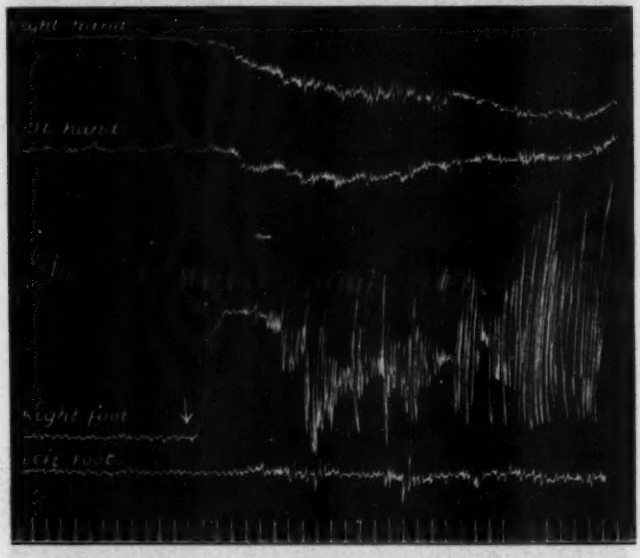

Fig. 5.—Development of latent intentional tremor.
Muscle tonus curves for the right and left upper and lower extremities. At +, the patient was asked to press his right foot against the pneumographic capsule with which it was connected. Tremor developed and was not confined to the left foot, but spread to the other extremities.

entire body, but in cases of slight or latent paresis of one of the upper or lower extremities, the tonus curves (usually already asymmetric) of the right and left sides show unequal reactions (Fig. 4*B*).

E. Tremor of Intended Movements.—Tremor which accompanies volitional movements becomes more pronounced the longer the movement lasts. In the finger-nose test, for instance, the tremor becomes more marked the closer the finger approaches the nose. Recording of the head movements which are too slight to be seen with the naked eye (*C*, Fig. 3) frequently shows the rotation factor to be the most pronounced. When the patient is sitting, the head may begin to tremble, since in this position the neck muscles are actively innervated. The tremor characteristic

of multiple sclerosis is not apparent in the extremities as long as they are relaxed; it may become evident when the patient is asked to press a hand or foot for some time against the pneumographic capsule with which it is connected (Fig. 5).

II. INITIAL SYMPTOMS IN THE VISUAL APPARATUS

In cases in which slight neurological signs outside the visual apparatus raise the suspicion of multiple sclerosis, but in which the clinical ophthalmologic methods usually applied (examination of the fundus, perimetric determinations, extraocular muscle balance studies, etc.) are noncontributory, special methods may be applied to reveal latent or slight ocular symptoms.

A. Nystagmus.—Latent nystagmus may become manifest when the patient is lying down or when while sitting he bends his head backward. Nystagmus not apparent in normal illumination may be observed when in a darkened room one or both eyes are illuminated by flashlight. Nystagmus developing under the latter condition may be physiological, and therefore must be evaluated with caution.

B. Examination of the Extraocular Muscles.—This examination forms part of the routine tests of the ophthalmologist and, consequently, will not be discussed in this paper.

C. Pupillography.—Pupillary signs are of special importance for the differential diagnosis of early cases of multiple sclerosis. As mentioned before, according to traditional teaching, pupillary responses are supposed to be rare in cases of multiple sclerosis. However, the results of pupillographic studies show that they are almost always present in more advanced cases and appear very frequently in early cases.

As discussed above, retrobulbar neuritis alone cannot establish the diagnosis of multiple sclerosis, although this disease is its most frequent cause. If, however, in cases with retrobulbar neuritis (or other signs, such as transient diplopia or nystagmus) pupillographic studies reveal additional lesions within the pupillary pathways, the multiplicity of symptoms may be indicative of multiple sclerosis.

Within the pathways of the pupillary contraction to light (Fig. 6), at least three different neurons (on each side) may be damaged independently: (1) from the retina to the pretectal area; (2) from the pretectal area to both the heterolateral and the ipsilateral third nerve nucleus, and (3) from the third nerve nucleus to the ciliary ganglion. Demyelination processes may be located in any of them. The dilation pathways from the cortex through the thalamus, hypothalamus, midbrain, metencephalon, and spinal cord include at least four, and probably more, intracerebral or intraspinal neurons on each side (Fig. 7). These eight neurons give theoretically the possibility of many independent lesions, quite a number of which occur practically and may be diagnosed pupillographically. This is shown in a few representative cases, in which syphilis was ruled out.

CASE 1.—*Lesion in the optic nerve.*

L. J., a woman aged 32, had always been nervous and high-strung, restless, and easily excited. Since childhood, she had suffered from frequent headaches, which were diagnosed as migraine headaches. During the months preceding examination, her general nervous condition became worse, and she started shouting and quarreling. Seven months before examination she saw spots in front of her left eye. Ophthalmologically, no pathological condition was found, and the symptom disappeared. Five months later, vision of the left eye became blurred, and a large central scotoma was found on the left side. The ophthalmological diagnosis was retrobulbar

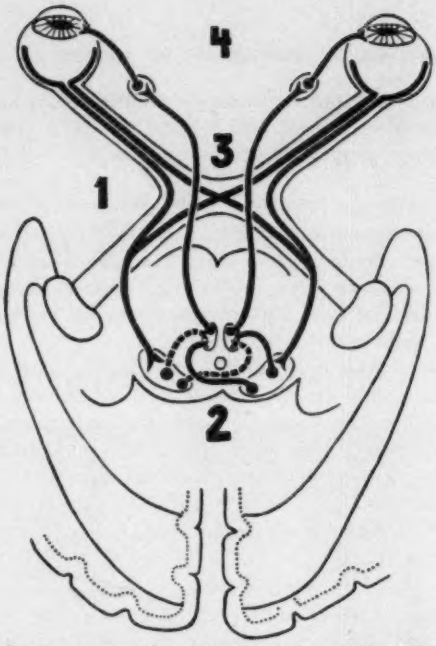

Fig. 6.—Scheme of neurons composing the pathway for pupillary light contraction.
1, from retina through optic nerve and optic tract to pretectal area (partial decussation in the optic chiasm); *2*, from pretectal area to homolateral and heterolateral third nerve nuclei (partial decussation in the posterior commissure); *3*, from third nerve nucleus to ciliary ganglion; *4*, from ciliary ganglion to sphincter pupillae.

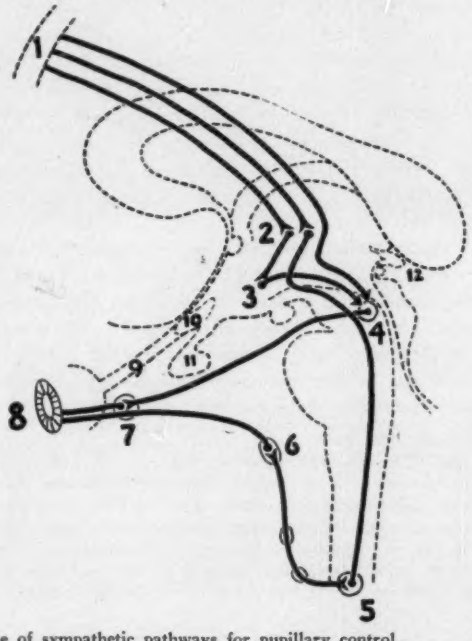

Fig. 7.—Scheme of sympathetic pathways for pupillary control.
(*1*) Area 8 of cerebral cortex, (*2*) thalamus, (*3*) hypothalamus, (*4*) third nerve nucleus, (*5*) Budge's center, (*6*) superior cervical ganglion, (*7*) ciliary ganglion, (*8*) iris, (*9*) optic nerve, (*10*) optic chiasm, (*11*) pituitary gland, (*12*) pineal body.

neuritis. X-ray examination of the skull and nasal sinuses, as well as tests of the blood and cerebrospinal fluid showed nothing pathological. Vision returned to normal after about two weeks.

At the time of the examination, the deep reflexes, particularly the ankle, patellar, biceps, and triceps reflexes, were hyperactive on the right side; vibration sense was slightly impaired in the right lower extremity; the "retention-of-position" test and muscle-tonus curves revealed slight paresis of the right lower extremity.

Since at this time a certain number of psychogenic symptoms had developed, doubts were expressed with respect to the organic nature of the previously diagnosed disturbances of vision. Therefore, pupillographic studies were done. They showed (Fig. 8) the pupils to be equal both at rest and in motion. However, light stimulation of the right eye resulted in direct and consensual contractions of 2.6 mm., while stimulation of the left eye resulted in direct and consensual reactions of only 2.0 mm. Throughout the series of reactions, the reflexes elicited from the left eye were less extensive than those elicited from the right eye, indicating that the conductibility of the left optic nerve was diminished; this confirmed a previously established, but later doubted, diagnosis of retrobulbar neuritis.

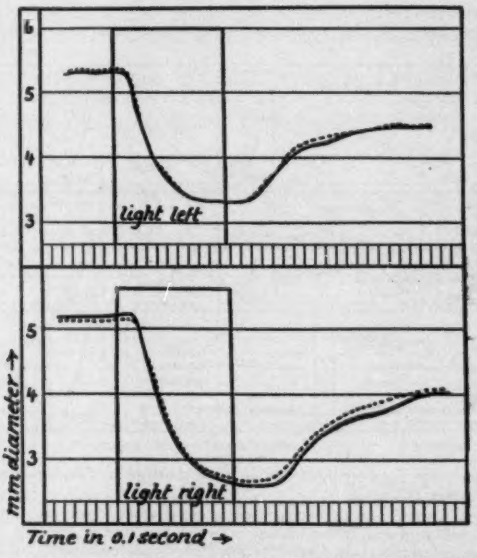

Fig. 8.—Pupillary reactions to light in a case of retrobulbar neuritis (Case 1). Both pupils react more extensively to stimulation of the right eye than to stimulation of the left eye.

Slight motor paresis of the right lower extremity with impairment of vibration sense in the same extremity, in connection with retrobulbar neuritis, justified the diagnosis of multiple sclerosis.

CASE 2.—*Lesion in the fibers connecting the pretectal area and the third nerve nucleus.* A. G., a woman aged 25, had never been sick before, but she had been tense and excitable since the age of 18. Six months before examination she momentarily saw double, with the right image higher than the left.

Neurological examination showed pyramidal symptoms: Ankle and patellar reflexes were hyperactive on the right side; abdominal reflexes, though all present, were hypoactive and exhaustible, especially the lower ones, and more on the right than on the left side; the "retention-of-position" test and muscle tonus curves of the lower extremities showed weakness of the right lower extremity.

Clinical ophthalmological examination revealed nothing abnormal except for hyperopic astigmatism.

Pupillographic examination (Fig. 9) showed anisocoria, with a difference of about 0.8 mm., which increased to about 1 mm. at the peak of the contraction, when the right (smaller) pupil was stimulated directly by light of average intensity, and decreased to practically zero when the left (larger) pupil was directly stimulated. The phenomenon was accentuated by prolonged or high-intensity illumination, indicating weakness of the consensual reaction to light in either pupil.

Since, normally, anisocoria cannot be induced by unilateral illumination,[10] these findings point to a second lesion—independent of the pyramidal lesion—situated in the connection fibers between the pretectal area and the third nerve nucleus. The diagnosis of multiple sclerosis was established by proving the existence of these two foci.

CASE 3.—*Lesion in the efferent pathway (third nerve).*

A. C., a woman aged 26, complained of blurred vision in her left eye when reading, a condition which had developed three weeks before. Her local physician had told her that she had a muscle imbalance.

Clinical ophthalmological examination showed the fundi to be normal; the left field was slightly constricted; there was no central scotoma; vision after correction was 20/20 in each

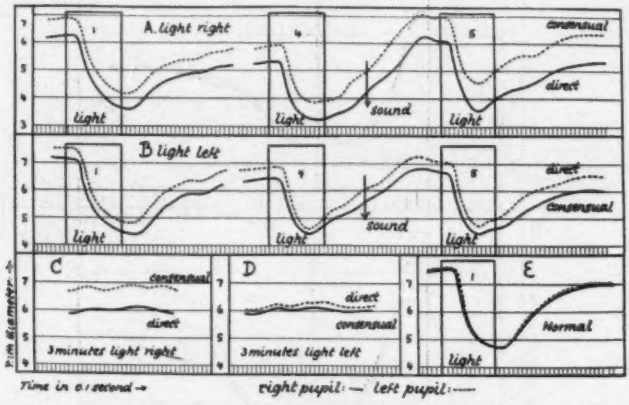

Fig. 9.—Pupillary reactions to light in case with damage to fibers connecting pretectal area and third nerve nucleus (Case 2).

A and *B:* First, fourth, and fifth reactions to light when right (*A*) and left (*B*) eyes are stimulated. A sound stimulus is interposed between the fourth and the fifth light reaction. Anisocoria increases when the right (smaller) pupil is stimulated directly and decreases when the left (larger) pupil is stimulated directly.

C: Increased anisocoria after three minutes of illumination of the right eye.

D: Disappearance of anisocoria after three minutes of illumination of the left eye.

E: Normal light reflex (for comparison). Direct and consensual reactions are identical.

eye; the left pupil was larger than the right and was slightly irregular at 10:30 o'clock; there was no atrophy of the iris.

Pupillographic studies (Fig. 10) showed that, after adaptation to darkness, the left pupil (7 mm.) was slightly larger than the right pupil (6.7 mm.). The reaction of the left pupil to light was sluggish and inextensive, amounting to no more than 1 mm., both on direct and indirect stimulation. The reaction of the left pupil to near vision was also slow and inextensive. Reactions of the right pupil to light and near vision were prompt and amounted to 3.5 mm. The shape of the reactions of the left pupil showed that the disturbance was parasympathetic,

10. Jones, I. S.: Anisocoria: Attempted Induction by Unilateral Illumination, Arch. Ophth. **42**:249-253 (Sept.) 1949.

concerned with the third nerve nucleus or the pathways peripheral to it. The fact that psychodilation was normal on both sides indicated that the lesion was central to the ciliary ganglion.[11]

Neurological examination showed pyramidal signs: Patellar and ankle reflexes were hyperactive on the right side, and the abdominal reflexes were almost absent.

The diagnosis was that of initial multiple sclerosis, since at least two independent lesions were demonstrable.

CASE 4.—*Lesions in the hypothalamus and in the fibers connecting the pretectal area and the third nerve nucleus.*

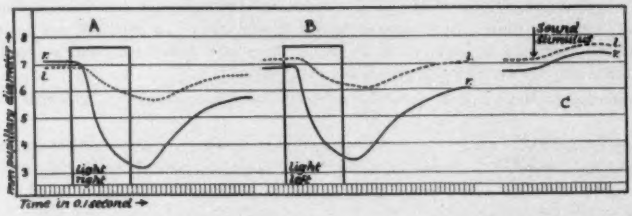

Fig. 10.—Pupillary reactions to light in a case with damage to the efferent pathway (third nerve) (Case 3).

A and *B.*: The reactions of the left (larger) pupil are sluggish and inextensive when either eye is stimulated.

C: Psychodilation in response to sound stimuli is present on both sides.

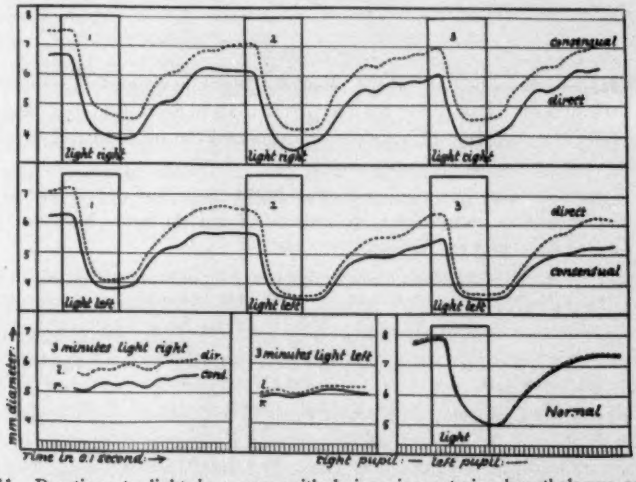

Fig. 11.—Reactions to light in a case with lesions in posterior hypothalamus and fibers connecting pretectal area and third nerve nucleus.

First and second lines: first, second and third reactions to light when the right (first line) and the left (second) line eyes are illuminated. From the beginning the reactions show the tonohaptic shape. Anisocoria increases when the right (smaller) pupil is stimulated directly and decreases when the left (larger) pupil is stimulated.

Anisocoria persists on illumination of the right eye for three minutes. Third line: disappears on illumination of the left eye for three minutes. Normal light reflex (for comparison).

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11. Lowenstein, O., and Loewenfeld, I. E.: Mutual Role of Sympathetic and Parasympathetic in Shaping of the Pupillary Reflex to Light: Pupillographic Studies, Arch. Neurol. & Psychiat. **64**:341-377 (Sept.) 1950.

M. L., a woman aged 30, had had bilateral nephritis at the age of 12. For the last two years migraine headaches had occurred once or twice a week, lasting for 24 hours, and accompanied with vomiting, pain in the back of the neck, and hypersensitivity to light; these symptoms improved when the patient rested in darkness. Three months before examination, she experienced prickling sensations in the left side of the lower lip and left side of the tongue, and pain in the left side of the face beneath the eye, particularly during the night. After some time these symptoms disappeared. Three days before examination she noticed slight weakness in her right hand, while playing the piano.

Neurological examination showed pyramidal symptoms: inexhaustible foot clonus on the right side; hyperactive patellar, ankle, biceps, and triceps reflexes, and a positive Hoffmann sign (flicking of one finger causes the other four to flex involuntarily) on the right side; ergographic studies showed increased fatigability of the right upper and lower extremities; muscle tonus curves showed slightly increased tonus on the right side.

Ophthalmological examination showed a clinically normal condition. Vision and fundi were normal.

Pupillographic studies (Fig. 11) revealed the following symptoms: (1) bilateral tonohaptic shape of the light reflexes, indicating a lesion in the posterior part of the hypothalamus or the midbrain cephalad to the third nerve nucleus [11]; (2) weakness of the consensual reaction to light when either eye was stimulated (cf. Case 2), pointing to a lesion in the fibers connecting the pretectal area and the third nerve nucleus.

Pyramidal symptoms in connection with lesions in two independent neurons within the pupillary pathways established the diagnosis of multiple sclerosis.

All clinical neurological symptoms disappeared within about four weeks. After a remission of eight years, during which the patient was apparently in good health, the disease recurred, with bilateral paresis of the lower extremities.

CONCLUSIONS

Methods are described by which clinically latent neurological symptoms may be revealed in cases in which ocular symptoms, such as retrobulbar neuritis and diplopia, raise the suspicion of multiple sclerosis and the usual neurological examination does not reveal corroborating signs.

These methods are concerned with the detection of low-degree paresis, latent tremor of the head or extremities, differences of muscle tonus between the right and left extremities, and nystagmus.

In cases in which symptoms outside the visual apparatus alone are insufficient to establish a diagnosis of multiple lesions, and ophthalmological examination shows a clinically normal condition, pupillography may reveal hidden symptoms which point to the presence of lesions in additional neurons, thereby making the diagnosis possible at an early date.

The development of general or ocular types of multiple sclerosis depends on the chance localization of the demyelination processes. Patients with two or more attacks of the disease usually show both ocular (including pupillary) and general symptoms.

CORNEAL DYSTROPHY FOLLOWING SECONDARY INTRAOCULAR OPERATIONS

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BULLOUS keratopathy is well known to occur in eyes with acute glaucoma, absolute glaucoma, and chronic iridocyclitis. This condition usually follows multiple operative procedures with persistent elevation of intraocular tension. This type of epithelial dystrophy has also been reported after cataract extraction in eyes with preexisting cornea guttata, or endothelial dystrophy, supposedly facilitated by trauma to the endothelium at the time of operation. However, there is no statistically significant series comparing the incidence of postoperative dystrophy in cases with and without preexisting endothelial change as determined by careful preoperative slit lamp examination. There have been no reports of corneal dystrophy following secondary intraocular operations upon eyes without prior endothelial dystrophy or postoperative glaucoma. It may be of interest, therefore, to report several cases in which epithelial edema and bullous keratopathy followed a secondary intraocular procedure upon an eye which had undergone previous intraocular operation for an acute attack of glaucoma. In each case no preexisting endothelial changes of the guttata type had been noted prior either to the primary or to the secondary operative procedure.

REPORT OF CASES

CASE 1.—Mrs. J. B., aged 62, had an acute attack of glaucoma in the left eye in November, 1937. An iridencleisis with sclerectomy was performed in another city. Ocular examination in September, 1938, revealed the cornea of each eye to be essentially normal. The anterior chambers were shallow, and the entrance to the angles was narrow. The patient suffered an acute attack of glaucoma in the right eye in September, 1938, and a Lagrange sclerectomy was done. The patient was examined periodically, and the intraocular pressure remained within normal limits without the use of miotics. Cataractous changes of the nuclear sclerosis type developed, and by 1947 they were sufficient to interfere with vision and warranted a cataract extraction. In August, 1947, an intracapsular cataract extraction was done on the left eye, the incision being made inferotemporally in order to avoid the functioning bleb above. Four weeks after the surgical procedure the patient had a corrected vision of 0.6, but striate keratopathy was still present. By January, 1948, the vision had decreased to perception of hand movements at 1 ft. (30 cm.), and the corneal changes were characterized by bullous keratopathy with bedewing of the corneal epithelium, limited to the lower two-thirds of the cornea. This condition is unchanged at the present time, and vasculogenesis is minimal. The intraocular pressure has remained normal without the use of miotics.

Presented at a meeting of the Chicago Ophthalmological Society, May 28, 1951.

From the Department of Ophthalmology of the Illinois Eye and Ear Infirmary, University of Illinois School of Medicine.

Case 2.—Mrs. P. C., aged 63, was referred for the treatment of acute glaucoma of the left eye in October, 1944. Ocular examination revealed the right eye to have a normal cornea but a very shallow anterior chamber. The picture of the left eye was that of typical acute glaucoma; with intensive use of miotics, the intraocular pressure was reduced to normal limits, and an Elliot trephination was done a day later. The patient was placed under treatment with miotics for the right eye. The operation for glaucoma of the left eye was unsuccessful, despite further therapy, the general course was downhill, and the eye was enucleated. The patient continued to use miotics in the right eye; nevertheless, an acute glaucomatous attack occurred in August, 1947. An iridencleisis was done superiorly after a scratch incision had been made and enlarged with scissors. The intraocular pressure remained normal without miotics. Vision was 0.8 until July, 1948, when the development of a cataract was noted. An intracapsular cataract extraction was done in December, 1948, an incision being made inferotemporally to avoid the area of the bleb. Corrected vision in January, 1949, was 0.5. Persistent striate keratopathy of the lower two-thirds of the cornea was noted after operation. In February, 1949, bedewing of the corneal epithelium was first noted. This developed into bullous keratopathy in several weeks, and vision was reduced to perception of hand movements at 1 ft. Vasculogenesis at the limbic area extended about 2 mm. into the cornea. The intraocular pressure remained normal without the use of miotics.

Case 3.—Mrs. A. F., aged 66, was seen for acute glaucoma of the right eye on March 31, 1948. Visual acuity was limited to counting fingers at 2 ft. (60 cm.). Marked superficial and deep ciliary injection was present. There was intense edema of the cornea, with much iris pigment on the posterior surface. The anterior chamber was shallow with a narrow entrance to the angle. The pupil was dilated to about 5 mm. The blood vessels of the iris near the pupillary border were dilated. *Glaucomflecken* were noted just beneath the anterior capsule of the lens. The optic disk and fundus were hazily seen but appeared normal. Examination of the left eye showed vision of 0.6, a normal cornea, a shallow anterior chamber, a clear lens, and no evidence of glaucoma.

There was no response to miotic therapy in this eye; so an iridencleisis was done superiorly, using an ab externo scratch incision enlarged with scissors. The nuclear sclerosis of the lens gradually increased sufficiently to warrant a cataract extraction. An intracapsular lens extraction, with an incision made inferotemporally, was done on Feb. 2, 1950. Striate keratopathy persisted for several months and was followed by bullous keratopathy and slight vasculogenesis at the corneal limbus. The intraocular pressure remained within normal limits without the use of miotics.

Case 4.—Mrs. K. B., aged 48, gave a history of an acute attack of glaucoma of the left eye, which was controlled with intensive miotic therapy, in May, 1945. At the time of examination, on May 10, the corrected visual acuity in this eye was 0.6. The eyeball was pale; the anterior chamber was shallow, with a narrow entrance to the angle apparent on gonioscopic examination, and the pupil was miotic. Tension was 53 mm. Hg (Schiøtz). The optic disk was normal. The patient was sent back to the referring physician with the recommendation that operation be performed upon the left eye. Later in May an iridectomy was performed at the upper limbus. Evidently this was unsuccessful, for iridencleisis was then performed at the superior temporal limbus. We saw the patient again in November, 1949, when complete bullous keratopathy without vascularization was present. Recurrent rupture of the epithelial blebs produced pain. Intraocular tension remained normal without miotics. A retrobulbar injection of alcohol was given on Jan. 12, 1951, with complete relief of symptoms and healing of the bullae, as of the present time.

The right eye had narrow-angle glaucoma, controlled with pilocarpine, with vision of 0.8 and a normal cornea.

Case 5.—Mrs. D. B., aged 50, had an attack of glaucoma in the left eye in 1931, for which an iridectomy was performed in the usual position. In February, 1934, vision in the left eye was 0.6, and examination showed a pale bulb, normal cornea, fine filtering scar above, shallow anterior chamber with a narrow, irregular operative coloboma of the iris above, diffuse anterior opacity of the lens, and normal optic disk. The intraocular tension measured 30 mm. Hg (Gradle-Schiøtz); so the patient was placed under treatment with pilocarpine, which controlled the tension. In September, 1945, the lenticular opacities became sufficiently dense that an intracapsular lens extraction was done at that time, with the use of McLean corneoscleral sutures and with the incision placed inferotemporally. Corrected vision the month following operation

was 0.5 and remained so until January, 1946, when the development of bullous keratopathy was first noted; this soon involved the entire cornea. No vasculogenesis of the cornea has been noted. The intraocular tension remained within normal limits with the use of 2% pilocarpine nitrate three times a day.

A functioning Elliot trephination had been performed on the right eye in 1924, with a normal cornea, shallow anterior chamber, diffuse anterior opacity of the lens, glaucomatous excavation and atrophy of the disk, tension of 15 mm. Hg (Gradle-Schiøtz), and vision of 0.1.

COMMENT

In these five cases, in which a previous operation for acute glacoma had been performed, bullous keratopathy followed secondary intraocular procedures—intracapsular cataract extraction by an inferotemporal approach in four cases and iridencleisis superotemporally in the fifth case. It is conceivable that the corneal endothelium may be damaged by the acute increase in intraocular pressure during the previous acute attack, rendering it more susceptible to injury by secondary operative procedures, with resulting corneal edema and bullous keratopathy. The incidence of bullous keratopathy after primary cataract extractions in our hands has been approximately 0.3%, while the incidence of this complication after secondary operations in nonglaucomatous patients has been approximately 0.8%. Bullous keratopathy following secondary operative procedures in patients who have had previous antiglaucoma surgery for acute glaucoma is approximately 8% in this series.

The small number of cases in this series makes one cautious in attempting to claim statistical significance or cause-and-effect relationships for this complication. Cogan,[1] in the third Francis J. Proctor Lecture, stated that the normal cornea is in a relatively deturgesced state by reason of the effective semipermeable membranes, the epithelium and the endothelium. The fluid within the corneal stroma is derived from the limbal blood vessels, and as long as the surface membranes of the cornea are intact and the fluids on the anterior and posterior surfaces of the cornea are hypertonic to that within the stroma, there will be a continuous net loss of water from the cornea, with subsequent deturgescence of the stroma. Transparency of the cornea is maintained by this deturgescence. Cogan has shown that damage to the corneal endothelium is a determining factor and will lead to edema of the cornea, with the development of bullous keratopathy.

Certain factors in cataract surgery after previous operation for glaucoma may aggravate the endothelial damage. Hughes [2] believes that the incidence of operative or postoperative complications, such as loss of vitreous, anterior synechias, and the contact of vitreous with the cornea (Reese phenomenon [3]) is greater when the lens extraction is done with the incision placed inferiorly. These complications, however, were not present in the cases previously described.

It may be of interest to comment on the fact that our patients were women.

It has been recognized that the occurrence of cataractous changes in the crystalline lens sufficient to interfere with vision is hastened by the surgical operation for an attack of acute glaucoma. This cataractous development evidently

1. Cogan, D. G.: Studies on the Clinical Physiology of the Cornea, Am. J. Ophth. **32**:625-633, 1949.

2. Hughes, W. F., Jr.: Personal communication to the authors.

3. Reese, A. B.: Herniation of the Anterior Hyaloid Membrane Following Uncomplicated Intracapsular Cataract Extraction, Am. J. Ophth. **32**:933-940, 1949.

is not due to direct surgical trauma to the lens. The problem deserves consideration, and it should be borne in mind that surgical intervention for the cataract extraction may be necessary later. A small incision, providing sufficient room for antiglaucoma surgery, made with a sharp instrument, such as the keratome, may be less traumatic to the corneal endothelium and may interfere less with the limbic circulation and, therefore, with corneal metabolism and nutrition. If an ab externo scratch incision is made, it should be enlarged only just enough to provide ample room for the performance of the surgical procedure. When a cataract extraction becomes necessary in an eye which has undergone previous intraocular surgery, the site of incision must be made so that additional trauma to the endothelium and interference with the limbic circulation are avoided. We have found that this can perhaps be done by making a limbus-based conjunctival flap to either side of the filtering bleb area. Two McLean corneoscleral sutures are inserted to each side and several millimeters from the bleb. The incision is made at the upper limbus, therefore, with formation of a conjunctival flap up to the area of the bleb; in the region of the bleb the incision is in the cornea anterior to the site of the previous antiglaucoma operation. We have used this modified technique for the cataract extraction upon three eyes which had had previous antiglaucoma surgery. The postoperative examination of the cornea in two cases showed no evidence of dystrophic changes; in one case, bullous keratopathy was noted only in the upper fourth of the cornea, and since this area is usually covered by the upper lid, the condition has not resulted in visual disturbance.

The edematous corneal epithelium may be dehydrated by the instillation of glycerin or hypertonic solutions. However, the effect is only transitory. When epithelial blebs rupture, the resulting irritation causes epiphora and further dilution of the tears, with lowering of the hypertonicity of the tear surface. Recently, Johnson and Nosik,[4] have proposed a resection of the greater superficial petrosal nerve to reduce the formation of tears, resulting in greater hypertonicity of the fluids on the corneal surface and withdrawal of fluid from the epithelial bullae. We have had no experience with this procedure. However, the retrobulbar injection of alcohol, which was done for one of the patients, has achieved completely satisfactory results up to the present time. The alcohol probably eliminates the sensory pain stimulus that is responsible for the increased tearing and thereby achieves the same physiological effect as resection of the greater superficial petrosal nerve, which eliminates the parasympathetic secretory fibers.

SUMMARY

Five cases are reported in which a previous operation for acute glaucoma had been performed and in which bullous keratopathy followed secondary intraocular procedures performed in a different quadrant of the limbus. These included four cataract extractions and one iridencleisis. It is postulated that the corneal endothelium may have been somewhat damaged by the acute increase in the intraocular pressure during the acute attack of glaucoma. Although the eyes responded well to the initial operation for glaucoma, secondary intraocular surgical procedure in another quadrant may have resulted in sufficient additional damage to the endothelium that the cornea became edematous and bullous keratopathy developed.

4. Johnson, L. V., and Nosik, W. A.: Greater Superficial Petrosal Neurectomy for Relief of Chronic Bullous Keratitis, A. M. A. Arch. Ophth. **45**:32-39 (Jan.) 1951.

BAND KERATOPATHY IN DISTURBANCES OF CALCIUM METABOLISM

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AND
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A FORM of band keratopathy, often accompanied with characteristic conjunctival changes, has been reported in 32 patients, by various authors.[1] All have shown definite or suspected evidence of abnormality in calcium metabolism. Among the entities producing this picture are sarcoidosis, hyperparathyroidism, renal disease, and vitamin D poisoning. Because this entity is rare, it seems worth while to present three cases observed by us. The first is that of a boy with renal rickets (renal osteodystrophy) who showed both corneal and conjunctival changes. This case is especially interesting in that even though large doses of calcium lactate and vitamin D were administered therapeutically, hypercalcemia was never demonstrated. The second case is that of a white man with sarcoidosis. The third case is that of a white woman with renal disease.

This ophthalmologic picture of disturbed calcium metabolism is one of a band opacity in the most superficial layers of the cornea, most pronounced in the limbal region and absent, or almost so, in the central portion of the cornea. The limbal band is described as being separated from the limbus by a clear area. The conjunctival changes have been characterized as consisting of frog-spawn-like nodules, some of which contain white flecks or crystals, thought to be calcium salts.

REPORT OF CASES

CASE 1.—J. M., a white boy aged 10 years, was admitted to Children's Hospital because of polydipsia and polyuria of a year's duration. Seven months prior to admission he had sudden onset of a painless limp. Systemic review revealed that the child had periods of nervousness associated with trembling. A nystagmus had been present since birth, and glasses had been prescribed at the age of 3 years.

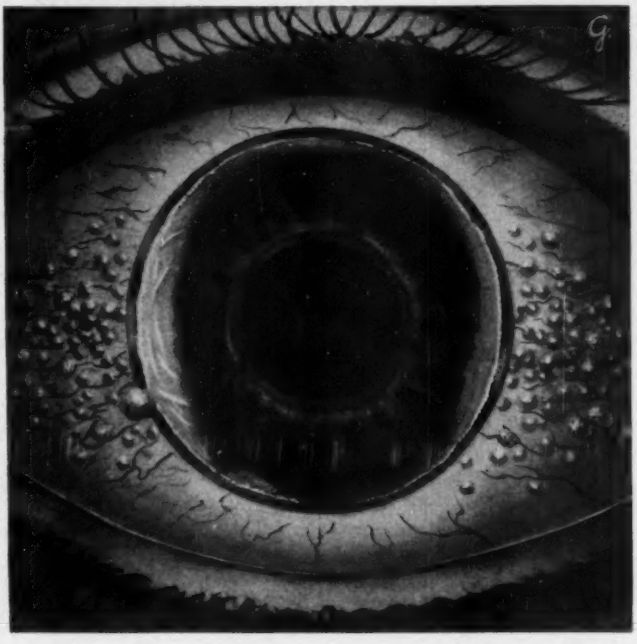
On physical examination, the child appeared apathetic and withdrawn. His skin was pale, and several ecchymotic areas were noted over his legs. The latter were emaciated, and a pronounced genu valgum was present. His gait was unsteady. Neurologic examination revealed nothing remarkable.

From the Department of Ophthalmology of the Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania.

1. (*a*) Cogan, D. G.; Albright, F., and Barter, F. C.: Hypercalcemia and Band Keratopathy, Arch. Ophth. **40**:624 (Dec.) 1948. (*b*) Walsh, F. B., and Howard, J. E.: J. Clin. Endocrinol. **7**:644, 1947. (*c*) Frost, J. W.; Sunderman, F. W., and Leopold, I. S.: Am. J. M. Sc. **214**:639, 1947. (*d*) Danowski, T. S.; Winkler, A. W., and Peters, J. P.: Ann. Int. Med. **23**:22, 1945. (*e*) Freeman, S.; Rhoads, P. S., and Yeager, L. B.: Toxic Manifestations Associated with Prolonged Ertron Ingestion, J. A. M. A. **130**:197 (Jan. 26) 1946.

Examination of his eyes revealed visual acuity of 6/30 in each eye with correction. The external condition was normal, as were the pupillary responses. There was a nondirected nystagmus, most marked on lateral gaze. Ophthalmoscopic examination of each eye revealed that the disk was pale and the vascular tree attenuated. The pigment of the peripheral fundi was conspicuously granular, but the foveal regions appeared normal. Peripheral fields were contracted generally to a 1/330 mm. white test object. These findings were thought to be compatible with the diagnosis of early tapetoretinal degeneration.

The red blood cell count was 2,140,000; the hemoglobin content was 5.5 gm. per 100 cc.; the specific gravity of the urine was 1.007, and the result of the Sulkowitch test [2] was negative. The reaction to a cutaneous tuberculin test was negative, as were the serologic reactions of the blood. The following serum values were found: carbon dioxide, 37 vol. %; chlorides, 109 mEq.; total protein, 6.8 mg.; nonprotein nitrogen, 120 mg., serum calcium, 10 mg., and phosphorus,



The salient features of each eye (Case 1) have been incorporated in this illustration. The thin white streaks on the left of the picture were seen only in the left eye.

6.8 mg., per 100 cc., and phosphatase, 26.4 Bodansky units. Urine concentration tests failed to obtain a specific gravity of over 1.012. A phenolsulfonphthalein test showed less than 5% of the dye to be excreted in each specimen.

Roentgenograms of the long bones and the skull showed marked decalcification and the typical picture of renal rickets. A retrograde pyelogram was normal.

The patient was placed on a low calcium diet in an attempt to distinguish between renal rickets and primary hyperparathyroidism. Since quantitative tests showed the urinary calcium to be low, the child was thought to have renal rickets. He was discharged with instructions to receive daily doses of 4 gm. of calcium lactate.

2. A qualitative test based on the precipitation of urinary calcium as calcium oxalate. If the result is positive, hypercalcemia is probably present.

A second admission occurred one month later. The laboratory findings were without significant changes. The serum calcium was 9.5 mg. per 100 cc. Three days later the patient was discharge with instructions to take daily doses of 50,000 U. S. P. units of vitamin D, in addition to the calcium lactate already prescribed.

Four and one-half months later the child was readmitted. There were no subjective changes, and the x-ray findings had not changed. The ophthalmologic examination at this time revealed an entirely new picture (Figure). The bulbar conjunctiva was moderately injected and appeared nodular in the intrapalpebral areas. A band keratopathy was present in each cornea. With slit-lamp magnification the conjunctival nodules appeared gelatinous. Some contained white flecks. The superficial portion of the cornea had an irregular, ground glass appearance, most intense near the limbus but fading centrally. Areas of haze did occur in both the superior and the inferior portion of the corneas, but these were not continuous with the horizontal areas, On the left cornea, particularly nasally, straight, thin, white streaks were noted in the epithelial region. A chain of white deposits was seen on the corneal side, running parallel to, but not continuous with, the limbus. These were similar in appearance to a Vogt white girdle. The ophthalmoscopic picture had not changed.

Repeated blood chemistry studies at this time showed the following variations: nonprotein nitrogen, 178 to 236 mg. per 100 cc.; calcium, 9.8 to 11.1 mg. per 100 cc.; phosphorus, 4.9 to 5.6 mg. per 100 cc. After several weeks the boy was sent home with directions to take the same doses of calcium lactate and vitamin D. Two months later, while in an ambulance en route to the Children's Hospital, the patient suddenly died. Postmortem examination was not performed.

CASE 2.—N. S., a white man aged 44, was admitted to the Hospital of the University of Pennsylvania [3] on Sept. 5, 1950, because of malaise and weakness for one and one-half years. He had noticed occasional pains in his shoulders, elbows, and interphalangeal joints. On a number of occasions he had passed small pieces of white material, "like soap powder," in his urine.

A year previously he had been admitted to another hospital. Because of a high serum calcium with a normal phosphorus level, normal skeletal calcification, and calcium deposits throughout the kidney parenchyma, a tentative diagnosis of hyperparathyroidism was made. Surgical biopsy of a nodule in the thyroid gland revealed normal parathyroid tissue.

Physical examination showed nothing remarkable except for palpable lymph nodes in the left axillary, cervical, and inguinal regions. Examination of the eyes revealed a visual acuity of 6/6 in each eye. A mild conjunctival injection was present, and the intrapalpebral conjunctiva appeared nodular. A band-shaped opacity was present in each cornea. A slit-lamp examination revealed the conjunctival nodules to have a gelatinous appearance; a few of these areas contained white flecks. Some of the nodules were astride the limbus, and even encroached on the corneal side. A superficial band type of opacity was present on the nasal and temporal sides of each cornea. In most of the areas of opacification there was no separation between the limbus and the beginning band opacity. The rest of the ophthalmologic examination showed nothing remarkable.

Laboratory findings were as follows: hemoglobin, 60 to 79%; red blood cell count, 3,200,000; white blood cell count, 7,800; blood urea nitrogen 32 to 44 mg. per 100 cc.; serum calcium, 12.8 to 14.4 mg. per 100 cc. The phenolsulfonphthalein test showed 8% excretion in 15 minutes and a total excretion of 33% in two hours. Acid and alkaline phosphatase were normal. The total serum protein was within normal limits, with slight increase in the euglobulin fraction. Urinalysis showed a few red blood cells and many white cells per high power field. The Sulkowitch test gave a 3+ reaction.

Roentgenograms of the chest showed a finely nodular infiltration throughout both lung fields. Abdominal films showed diffuse, as well as localized, calcinosis of both kidneys. A bone survey showed multiple calcium deposits in the soft tissues about the shoulders and hip joints. No demineralization of the bones was noted.

The patient was placed on a low calcium diet; a low urinary excretion of calcium under this regimen was thought to be evidence against hyperparathyroidism. A biopsy of axillary lymph nodes revealed changes compatible with a diagnosis of sarcoidosis.

3. The patient was referred for consultation by Dr. Francis C. Wood.

CASE 3.—D. D., a white woman aged 26, was admitted to the medical ward of the Hospital of the University of Pennsylvania on April 30, 1951, complaining of weakness and tiredness, frequent aches about the joints, and headaches of two or three years' duration. She had vomited on several occasions during the two or three months prior to admission. Although the patient had had frequent urinalyses for many years by a former physician, she was unaware of any specific renal disease.

Physical examination revealed a small corneal opacity on the left eye. The thyroid was palpable, and perhaps slightly enlarged, and a venous hum was heard in the neck on the right side. There was a soft pulmonic systolic murmur. Tenderness in the costovertebral angle was present bilaterally.

Ocular examination revealed corrected visual acuity of 6/6 in the right eye and 6/12 —1 in the left eye. A corneal scar covered the line of vision in the left eye. The conjunctiva was normal except for yellowish nodular deposits immediately adjacent to the limbus in each eye on both the temporal and the nasal side. The reactions of the pupils were normal, as were those of the extraocular muscles.

The slit-lamp examination of the right eye revealed a normal anterior segment except for groups of clear nodules in the interpalpebral spaces on the conjunctival side of the limbus. Some of these nodules contained white flecks at their apexes. The conjunctiva between the nodules in these areas appeared somewhat yellowish. The left eye showed similar changes. The ophthalmoscopic picture was normal.

Significant laborataory findings were as follows: hemoglobin, 58%; red blood cell count, 3,700,000; white blood cell count, 7,400; blood urea nitrogen, 57 to 80 mg. per 100 cc.; serum calcium, 10.5 to 10.6 mg. per 100 cc.; alkaline phosphatase, 75.2 to 81.0 Shinowara units; carbon dioxide, 36 vol. %; chlorides, 107 mEq. Serum sodium and potassium were normal. Urinalysis showed a 1+ reaction for albumin and occasional white blood cells. The urinary calcium excretion was within normal limits. Serologic tests for syphilis gave negative reactions. X-ray examination of the chest showed no evidence of pulmonary disease. There were cystic changes in the ribs and right clavicle compatible with the diagnosis of hyperparathyroidism. Demineralization of the skull, with absence of the lamina dura in all the teeth, was noted. Some of the vertebrae had a biconcave appearance. Demineralization and cystic changes were present in the pelvis, in each humerus, and in the femurs. Both kidney shadows were small. No dye was seen at any time after an attempted intravenous urogram.

The patient was seen in the department of urology. It was suggested that her hyperparathyroidism was probably secondary to renal disease. Members of the department of endocrinology also saw the patient, and the opinion was expressed that her hyperparathyroidism was secondary to renal disease because of the previous history of repeated urinalyses, the severe renal impairment, the small, shrunken appearance of the kidneys on x-ray examination, absence of visible renal calcinosis or calculi, the high level of the phosphates, the normal serum calcium (although on two occasions elevated serum calcium had been reported at a previous hospital), and the normal urinary excretion of calcium.

COMMENT

The first two patients reported here showed the typical band keratopathy and associated conjunctival nodules described in patients with disturbance in calcium metabolism. It is of interest, but probably of little significance, that a clear area between the limbus and the corneal opacities, as reported in the previous literature, was not present. As the cornea was not involved, only conjunctival nodules were seen in the third patient.

The corneal and conjunctival changes are thought to result from the deposition of calcium in these tissues, secondary to hypercalcemia. Walsh and Howard [1b] reported that chemical analysis of a biopsy specimen of the abnormal conjunctiva revealed the presence of what was probably a calcium salt. An associated finding in many of these cases has been nephrocalcinosis or nephrolithiasis, and it had been postulated that the mechanism of deposition is probably similar. The findings in our second case fit into this concept with no difficulty. However, no hyper-

calcemia or evidence of other tissue calcium deposition was noted in the child with renal rickets. In our third case hypercalcemia was not found while the patient was in our hospital, but the calcium level had been reported elevated previously by another laboratory.

Renal rickets is an entity associated with renal disease in which the kidney tubules are so damaged that they are no longer able to manufacture sufficient base (ammonium) with which to excrete acids. Calcium may be utilized as a substitute for the ammonium radical. Thus, the serum calcium tends to fall, with a resulting parathyroid hyperplasia. However, because of the glomerular damage, the parathyroid hormones cannot result in a phosphorus diuresis; hence, calcium is deposited in the osteoid tissue. The essential bone lesion in renal rickets is one of destruction, rather than of lack of calcification of the osteoid tissue. In view of the loss of calcium from the body, via the kidneys, increased oral calcium is given along with vitamin D to promote the absorption of calcium from the intestine.[3a]

Although high serum calcium values were not demonstrated in our case of renal rickets, it is not impossible that periods existed when the serum calcium was increased. On the other hand, the combination of irradiated ergosterol and calcium lactate may have been the factor responsible for the deposition of calcium. Many of the toxic manifestations of ergosterol have been thought to be secondary to metastatic tissue calcification.[1c-e] There are some [4] who believe that it is the calcium given concomitantly with the ergosterol which is responsible for the degree of hypercalcemia, with resultant tissue calcification. It may be, of course, that an abnormal calcium movement between tissues and serum, rather than the hypercalcemia per se, results in the metastatic phenomena. Cogan and associates [1a] also reported a case of band keratopathy in a patient in whom high serum calcium values were never found.

SUMMARY

Three patients with abnormal calcium metabolism showing conjunctival changes, associated with a band keratopathy in two instances, are reported. It is suggested that the findings may be due to an abnormal mobilization and transport of calcium which results in the metastatic calcification, rather than in the hypercalcemia itself.

3a. Albright, Fuller, and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease, Baltimore, Williams & Wilkins Company, 1948.

4. Bauer, W., and Aub, J. C.: Am. J. Dietetic A. **3**:106, 1927.

STUDIES ON THE CRYSTALLINE LENS

IV. Distribution of Cytochrome, Total Riboflavin, Lactate, and Pyruvate and Their Metabolic Significance

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DETROIT

THE ENZYME systems involved in the respiration of the lens have not been established. Whereas many attempts have been made to demonstrate that the same enzymes—flavoprotein and cytochrome-cytochrome oxidase [1]—which catalyze oxygen uptake in other tissues also function in this capacity in the lens, the only direct evidence, to our knowledge, for the existence of a flavoprotein or a cytochrome-cytochrome oxidase system in the lens is that obtained by Philpot and Pirie.[2] These authors reported two analytical values for the riboflavin content of the lens. Using the microbiologic method of assay, they found that lenses devoid of capsule, and presumably therefore of epithelium, contained in the two instances 0.05 and 0.12 γ of riboflavin per gram of wet weight. Other investigators [3] failed to detect riboflavin or flavoprotein in the lens by fluoroscopic methods.

Von Euler and Günther [3b] and Burdon-Cooper and Lewis [4] were unable to demonstrate the presence of cytochrome c in the lens, and the former authors could not find cytochrome oxidase. As a consequence, von Euler and co-workers [3c] postulated that a new oxidation-reduction system might be operative in the lens which could take the place of the flavoprotein and cytochrome systems. Evidence for the existence of such an enzyme system, either in the lens or in other body tissues, has not been presented.

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1. Coenzymes I and II are present in the lens (von Euler, H.; Hellström, H.; Schlenk, F., and Günther, G.: Die Enzymsysteme des oxydo-reduktiven Stoffwechsels in Augenlinsen, von Graefes Arch. Ophth. **140**:116, 1939). This fact does not indicate that the usual respiratory system operates in the lens, since these enzymes also participate in anaerobic metabolism.

2. Philpot, F. J., and Pirie, A.: Riboflavin and Riboflavin Adenine Dinucleotide in Ox Ocular Tissues, Biochem. J. **37**:250, 1943.

3. (*a*) Rochat, G. F.: Ist das Laktoflavin in einer einzigen menschlichen Linse nachweisbar? Klin. Monatsbl. Augenh. **103**:432, 1939. (*b*) von Euler, H., and Günther, G.: Zur Kenntnis des Diaphorase-Vorkommens im Blut und in Augenlinsen, Ztschr. physiol. Chem. **256**:229, 1938. (*c*) von Euler, H.; Hellström, H.; Schlenk, F., and Günther, G.: Die Enzymsysteme des oxydo-reduktiven Stoffwechsels in Augenlinsen, von Graefes Arch. Ophth. **140**:116, 1939.

4. Burdon-Cooper, J., and Lewis, S. J.: The Mineral Constituents of Cataractous and Normal Lenses and the Like, Transactions XIII Concilium ophthalmologicum, Amsterdam, September, 1929, Vol. I, p. 185.

More recently, Ely and Robbie [5] also reported that in no case were they able to detect cytochrome c in either rabbit or bovine lenses. However, Herrmann and Moses [6] obtained indirect evidence that cytochrome oxidase may be present in the lens by observing that the oxidation of hydroquinone by homogenates of bovine lenses was greatly accelerated by the addition of cytochrome c.

Despite the paucity of direct experimental evidence for the participation of a cytochrome system in the respiration of the lens, the observation that 90% of its oxygen uptake can be inhibited by cyanide [5] suggests that some heavy metal catalyst is operative in the lens. The most likely compound would appear to be cytochrome c. Failure to find this substance may be ascribed to the use of the whole lens for analysis, a procedure which, if cytochrome were present in but a small fraction of the lens, might so reduce its concentration that it could not be detected. Indeed, this possibility was mentioned by Dische, in discussing the paper of Ely and Robbie. We believed it worth while to reinvestigate the nature and distribution of respiratory enzymes in the lens, using three constituent parts for analysis.

METHODS AND MATERIAL

Various parts of the adult rabbit and bovine lenses, and one human lens which was removed for senile cataract, were used for analysis. These parts consisted of a combination of the epithelium and capsule, the cortex, and the nucleus; they were separated by gross dissection. (The epithelium was shown to adhere to the anterior portion of the capsule by staining with Nadi reagent.)

Lenses of all three species were used for the qualitative determination of the cytochrome-cytochrome oxidase system. Only bovine lenses were employed for the quantitative analysis of both cytochrome c and riboflavin because the large number of epithelia required made the use of rabbits prohibitive. Rabbit lenses were used for the determinations of lactate and pyruvate, as only single samples were required and specimens could be obtained immediately after death of the animal.

The weight of the epithelium of an adult rabbit lens was calculated from measurements of its thickness and area, as determined in histologic sections, to be approximately 0.5 mg.; that of the bovine lens was estimated from published values of the thickness of the epithelium and the diameter of the lens to be approximately 2 mg. These two values were used for computing the concentration of the various substances observed in the epithelium.

Cytochrome-cytochrome oxidase was determined qualitatively by staining with Nadi reagent. This reagent was prepared immediately prior to use by mixing equal volumes of freshly prepared solutions of 0.01 molar dimethyl paraphenylenediamine and 0.01 molar alpha-naphthol. Several drops of the reagent were placed on either a cross section of the lens or the separated epithelium-capsule combination. The appearance of the deep color of indophenol blue indicates the presence of the cytochrome system. Failure of the color to develop in the presence of cyanide, which poisons this system, is further evidence of specificity.

Cytochrome c was determined quantitatively in an extract of the epithelium-capsule combination from 40 bovine eyes by measuring the amount of absorption at 415 mμ in a Beckman spectrophotometer. The extract was prepared by the procedure outlined by Stotz,[7] and the identity of the compound was established by comparing the absorption peaks of the extract with the established peaks for cytochrome c. No appreciable amounts of compounds which would interfere with the absorption measurements were observed.

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5. Ely, L. O., and Robbie, W. A.: The Cyanide Sensitivity and Cytochrome-C Content of the Crystalline Lens, Am. J. Ophth. **33**:269, 1950.

6. Herrmann, H., and Moses, S. G.: The Cytochrome Oxidase Activity of the Lens of the Bovine Eyes, J. Biol. Chem. **158**:47, 1945.

7. Stotz, E.: The Estimation and Distribution of Cytochrome Oxidase and Cytochrome C in Rat Tissues, J. Biol. Chem. **131**:555, 1939.

Two analytical methods were used for the determination of riboflavin. The first was an adaptation of the fluorometric method of Fujita and Matsuura.[8] The various parts of the lens were ground separately in a Potter-Elvehjem tissue homogenizer. Each sample was heated to 80 C. for 15 minutes to inactivate phosphatase, and the proteins were then precipitated at pH 4.5 at the same temperature. The resulting supernatant was washed three times with chloroform in an attempt to remove interfering fluorescent materials. The sample was made alkaline and irradiated with visible light to convert any riboflavin which might be present to lumiflavin. Interfering substances soluble in chloroform were again removed by extraction. (The alkaline form of lumiflavin is insoluble in chloroform.) The solution was then made acid, and the lumiflavin was extracted with chloroform and measured fluorophotometrically with an especially sensitive instrument which contained a photomultiplier tube. An unirradiated sample served as a blank. A sample of tissue to which a known amount of riboflavin had been added was irradiated, extracted, and measured in the same manner. This sample served as a standard.

The second procedure employed for analysis of riboflavin was the microbiologic method of Lowry and Bessey.[9] For convenience, the amounts of materials used by these authors were increased tenfold in the present determinations. The epithelium-capsule combination from 34 bovine lenses and the cortex and nucleus from one lens were employed for analysis.

Lactic and pyruvic acids were determined by the colorimetric methods of Barker and Summerson[10] and Bueding and Wortis,[11] respectively. The lenses were removed from rabbits immediately after death; the epithelium-capsule combination, cortex, and nucleus were dissected free, and the tissues were ground as rapidly as possible.

RESULTS

The addition of several drops of Nadi reagent to sections of rabbit and bovine lenses cut anteroposteriorly through the middle produced an intense blue color in the anterior part of the lens. The color was confined to the epithelium and was not observed in the capsule or in the region of the equator, where cells derived from the epithelium are present. A blue color also appeared when the Nadi reagent was dropped on the epithelium-capsule combination of the rabbit and bovine lenses and the human cataractous lens. In all instances the color was confined to the epithelium. The addition of cyanide to the epithelium-capsule combination before application of the Nadi reagent prevented the formation of the blue color. These results indicate the presence of the cytochrome-cytochrome oxidase system in the epithelium.

As the cortex and nucleus of the lenses did not stain with Nadi reagent, quantitative analysis for cytochrome c was made only on the epithelium-capsule combination. An average of 4.3 γ of cytochrome c was isolated from the epithelium-capsule combination of each bovine lens. It is probable that the cytochrome c was derived from the epithelium, since the capsule did not stain with the Nadi reagent. The concentration of cytochrome c in the epithelium calculated on the basis of this assumption was 200 mg. per 100 gm.

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8. Fujita, A., and Matsuura, K.: Determination of Free and Esterified Riboflavin by Lumiflavin, J. Biochem. **37**:445, 1950.

9. Lowry, O. H., and Bessey, O. A.: A Method for the Determination of 0.5 to 2 Millimicrograms of Riboflavin, J. Biol. Chem. **155**:71, 1944.

10. Barker, S. B., and Summerson, W. H.: The Colorimetric Determination of Lactic Acid in Biological Material, J. Biol. Chem. **138**:535, 1941.

11. Bueding, E., and Wortis, H.: Stabilization and Determination of Pyruvic Acid in the Blood, J. Biol. Chem. **133**:585, 1940.

The attempts to determine the riboflavin content of various parts of the lens by fluoroscopic methods were unsuccessful. The results are, nevertheless, of some interest and will be reported here as a possible guide to others who may wish to investigate flavines or other fluorescing substances in the lens.

Chloroform extracts of homogenized samples of the epithelium-capsule combination and the cortex of bovine lenses exhibited an intense blue fluorescence, the former sample showing considerably more fluorescence than the latter. (The protein precipitate of the sample of nucleus was incomplete, so that the determination of riboflavin in this part of the lens was not continued.)

The chloroform extract obtained from the alkaline solutions of the epithelium-capsule combination and the cortex after irradiation also exhibited blue fluorescence, even though all blue fluorescent material had been extracted before irradiation. Chloroform extracts of the samples after acidification also fluoresced intensely blue-

TABLE 1.—*Content of Total Riboflavin in the Epithelium, Cortex, and Nucleus of the Bovine Lens*

	Millimicrograms/Lens	Average, Mg./100 Gm.
Epithelium *	5.6; 5.1; 5.7	0.28 †
Cortex	32; 34	0.003
Nucleus	<0.25	<0.00006

* It is assumed that all the riboflavin observed in the epithelium-capsule combination is confined to the epithelium.
† Calculated on the assumption that epithelium weighs 2 mg.

TABLE 2.—*Content of Lactate and Pyruvate in the Epithelium, Cortex, and Nucleus of the Rabbit Lens as Compared with That of Several Other Tissues*

Tissue	Lactate, Mg./100 Gm.	Pyruvate, Mg./100 Gm.	Lactate-Pyruvate Ratio
Lens epithelium	25 ± 9.9* (6)†	500 ± 120 (10)	0.05
Lens cortex	181 ± 39 (7)	5.3 ± 1.7 (10)	25.0
Lens nucleus	120 ± 42 (7)	10.8 ± 2.3 (10)	12.0
Liver (rat)	12.1	2.9	4.2
Kidney (rat)	10.8	2.45	4.4
Muscle (rat)	8.3	2.2	3.8

* Standard deviation.
† Number of determinations.

white, thus completely masking any yellow-green fluorescence due to lumiflavin which might have been present. The standard to which pure riboflavin had been added also did not exhibit the yellow-green fluorescence characteristic of lumiflavin, with or without the use of interference and auxiliary optical filters selected to eliminate the chief blue components.

The use of the microbiologic method of assay for riboflavin was more satisfactory than the fluorescent method of analysis. The results, which are presented in Table 1, show that riboflavin is present in various parts of the lens, its concentration being approximately 100 times as great in the epithelium as in the cortex. Little, if any, riboflavin is present in the nucleus.

The concentration of lactate and pyruvate in the epithelium,[12] cortex, and nucleus of the rabbit lens are shown in Table 2, along with values for liver, kidney, and

12. The pyruvate and lactate observed from analyses of the epithelium-capsule combination were ascribed to the epithelium, since neither substance could be detected in the posterior part of the capsule, where epithelium is not present.

muscle obtained by one of us (C. F.) in another study.[13] The data show that the epithelium contains an unusually high concentration of pyruvate and a low concentration of lactate, whereas the cortex and nucleus contain an unusually high concentration of lactate and a low concentration of pyruvate. The magnitude of the difference is evident from a comparison of the ratios of lactate to pyruvate for the various parts of the lens.

COMMENT

The results of the present study indicate that both the flavoprotein and the cytochrome-cytochrome oxidase enzyme system are present in the lens [14] and that they exist in much greater concentration in the epithelium than in the cortex or nucleus. Their distribution is similar to that observed by Friedenwald and Stiehler [15] for cytochrome c in the ciliary body and by Bessey and Lowry [16] for riboflavin in the cornea.

The cytochrome and riboflavin systems in the epithelium of the lens appear to be functioning in the oxidation of carbohydrate, and not solely in the oxidation of amino acids or fats. This deduction can be drawn from a consideration of the difference between the ratio of lactate to pyruvate in the epithelium (where cytochrome oxidase is present) and the ratio in the cortex and nucleus (where this enzyme appears to be absent). The lactate-pyruvate ratio in the epithelium is approximately only one five-hundredth and one two-hundred-fiftieth that in the cortex and nucleus, respectively (Table 2). In other words, the concentration of pyruvate in the epithelium is much greater than that in the deeper portion of the lens, and the concentration of lactate is less. That these differences in the lactate-pyruvate ratio may be ascribed to the functioning of cytochrome oxidase in the metabolism of carbohydrate in the epithelium, and not in the remainder of the lens, is apparent from a consideration of the steps involved in the breakdown of glucose. In the absence of cytochrome oxidase, the hydrogen atoms which have been removed by diphosphopyridine nucleotide during the conversion of a molecule of glucose to two molecules of pyruvate cannot combine with oxygen, and so must combine with pyruvate to form lactate if metabolism is to continue. In the presence of cytochrome oxidase, some of these hydrogen atoms unite with this enzyme and react with oxygen to form water. Thus, in a system in which cytochrome oxidase either does not participate in carbohydrate metabolism or is lacking (as in the cortex and nucleus), the amount of lactate formed would be greater than that in a system in which cytochrome oxidase functions in oxidation of carbohydrate. The deficiency of lactate in the epithelium as compared with that in the cortex or nucleus thus indicates that the cytochrome oxidase present is functioning, in part at least, in the breakdown of carbohydrate.

13. Frohman, C. E.; Orten, J. M., and Smith, A. H.: Chromatographic Determination of the Acids of the Citric Acid Cycle in Tissues, J. Biol. Chem., to be published.

14. From the similarity of results of the qualitative tests for cytochrome c in the epithelium of the rabbit and bovine lenses, it seems probable that the content and distribution of riboflavin in these two lenses are also similar.

15. Friedenwald, J. S., and Stiehler, R. D.: Circulation of the Aqueous: VII. A Mechanism of Secretion of the Intraocular Fluid, Arch. Ophth. **20**:761 (Nov.) 1938.

16. Bessey, O. A., and Lowry, O. H.: Factors Influencing the Riboflavin Content of the Cornea, J. Biol. Chem. **155**:635, 1944.

The lens epithelium appears to have a strictly aerobic type of metabolism, and the cortex and nucleus seem to have a strictly anaerobic type, as compared with such other tissues as liver, kidney, and muscle. This conclusion may also be drawn from the extreme difference in the lactate-pyruvate ratios (Table 2).

The epithelium seems to consume oxygen at an unusually rapid rate. Assuming that most of the oxygen uptake of the lens occurs in the epithelium (an assumption which seems justified from the results of the present study), the QO_2 (cubic millimeters of oxygen consumed per milligram of dry weight of tissue per hour) of this tissue would be approximately 90, i. e., 1,000 times that for the whole lens (0.09) reported by Ely and Robbie, since the weight of the epithelium is but one-thousandth that of the whole lens. This value, while admittedly only approximate, nevertheless suggests that the rate of respiration of the epithelium is extremely high in comparison with other tissues, for example, the liver, which has a QO_2 of 7.[17]

Thus, the respiratory enzymes which have been shown to be present in the epithelium of the lens give rise to an apparently completely aerobic type of metabolism, the rate of which appears to be unusually rapid, while the observed deficiency of respiratory enzymes in the cortex and nucleus permits only anaerobic metabolism. Since by far the greater amount of energy derived from the breakdown of carbohydrate is obtained aerobically, the fundamental differences in metabolism in the various parts of the lens suggest that an important, if not the sole, function of the epithelium may be to provide energy for the maintenance of the entire lens—a not insignificant role considering their relative size and protein content. The possible mechanism by which energy may be transferred to and utilized by the cortex and nucleus will be treated in a subsequent publication.

SUMMARY

The existence of a flavoprotein and a cytochrome-cytochrome oxidase enzyme system in the lens has been demonstrated. These respiratory enzymes are much more concentrated in the epithelium than in the cortex or nucleus. The ratio of the concentrations of lactate and pyruvate in the various parts of the lens indicates that the enzymes are functioning in the oxidation of carbohydrate and that the metabolism of the epithelium is strictly aerobic while that of the cortex and nucleus is strictly anaerobic. These observations suggest that an important, if not the only, role of the epithelium may be to provide energy for the maintenance of the entire lens.

Dr. Elek Ludvigh made the fluoroscopic determinations. Dr. Harold Zweng determined the weight of the epithelium of the rabbit lens. Misses Eileen Horgan and June Twomey and Mrs. Barbara Zolliker gave technical assistance.

Dr. C. W. Christensen, of Difco Laboratories, Inc., Detroit, supplied the strain of Lactobacillus casei.

17. Dickens, F., and Greville, G. D.: Metabolism of Normal and Tumour Tissue: VIII. Respiration in Fructose and in Sugar-Free Media, Biochem. J. **27**:832, 1933.

EXPERIMENT IN WHICH FIFTY PRESBYOPES WERE PROVIDED WITH TRIFOCAL GLASSES

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ARTICLES have appeared in popular magazines and newspapers suggesting trifocal glasses for general use.[1] Manufacturers report a sharp increase in sales and now suggest that most wearers of bifocals would be better satisfied with trifocals. Nothing in the textbooks or the literature suggests the use of trifocal glasses except in certain occupational groups.[2] Ophthalmologists otherwise prescribe trifocals only when requested.

In order to provide evidence as to whether presbyopes of all degrees and of all occupations would benefit by the use of trifocal glasses, I have during the past year made available to all my presbyopic patients trifocals at the same price as bifocals.[3] The patients were assured that if they found trifocals objectionable in any way, bifocals would be supplied free of charge. Most patients were interested, and 50 tried them.

Except for the experiment, probably none of these patients would have obtained trifocals. Frankly, I expected trouble, and my optician expected trouble. Our fears proved unfounded. I expected to spend too much time explaining the use of trifocals to patients. Use of the trifocal trial lens set proved sufficient to explain the effect and desirability of trifocals to the patient. The only additional time required was for comparison of intermediate distance vision with bifocal trial lenses.

Additional data were obtained for future use: extent of clear vision in the three distance ranges, depth of focus at three fixation distances, vertex distance from lens to cornea, and estimated pupil size.

PROCEDURE

The distance refraction was obtained in the usual way. The trifocal test lenses were in rings to fit the trial frame. The distance portion had zero power, and the intermediate segment had 50% of the total addition required for near vision (to be called the "add"). The maximum segment width of these flat-top trifocals was 22 mm. These trial lenses were placed in the frame cell nearest the eyes, to provide projection of as large a reading area as possible. The visual field was restricted by the 23 mm. diameter of my precision trial lenses, but this was no real handicap.

From the Oscar Johnson Institute and the Department of Ophthalmology of the Washington University School of Medicine.

1. Bedell, E.: Trifocals, Today's Health (formerly Hygeia) **28**:18-19 (Nov.) 1950. Springer, J. L.: "CV" Glasses for Better Vision, Coronet, p. 62, Sept., 1951.

2. Spillman, R.: Trifocal Glasses as an Aid to the Older Roentgenologist, Am. J. Roentgenol. **61**:102, 1949.

3. Financed by a grant in aid from the Univis Lens Co., Dayton, Ohio.

A near-vision card with two sets of test type was used. One set provided a lower line of type with a visual angle of 5 minutes at a distance of 40 cm., and the other an equal visual angle type for a distance of 80 cm. For testing the ranges of clear vision through the three parts of the lenses, the patient was instructed to watch the lowest letters easily visible.

The card was supported by the left hand, which could move along one end of a meter stick, while the other end was held with the right hand at the patient's outer canthus. The blur point for near vision, or the approximate limit of accommodation, was tested monocularly to judge balance. Other ranges of clear vision were measured binocularly.

If the three ranges did not seem adapted to the patient and his requirements, the test was repeated with different powers for near. With the proper add for a distance selected by the patient, he should report equal blur from binocular +0.50 D. and —0.50 D. spheres (hereafter written simply as + or —0.50) presented alternately. In other words, the visual distance to which the lenses are adapted should be approximately equidistant from the blur point for near and that for far vision.

The patient observed the binocular jump, or shock to convergence in gaze from distance to near, through bifocals as compared with that through trifocals. This difference was said to be analogous to stepping up onto a table, or to taking a step first onto a chair, then to the table. It was found helpful to explain how trifocals adapt the eyes to observation of a large newspaper held before the eyes. The headlines at a distance of about 1 meter can be seen through the distance portion of the lens; the body of the paper at a nearer distance, through the intermediate segment, and the fine print near the eyes, through the lower segment. Such vision comes naturally without nodding the head, or projection and retraction of the head characteristic of those wearing bifocals with a strong add.

RESULTS

When a patient was given a view through bifocal trial lenses after use of trifocals, he found the intermediate blur surprising and objectionable. He then required no further explanation.

Of the 50 patients receiving trifocal glasses, 12 had never worn bifocal glasses, and several had never worn glasses at all. Not one of these patients had trouble "breaking in" trifocal glasses. Of 50 patients, 14 required an add of + 2.50; 13, of + 2.25; 7, of + 2.00; 10, of + 1.75; 1, of + 1.50, and 5, of + 1.25. Those with poor results came from no particular group, and those reporting good results came from all groups.

Four of the 50 patients decided to change back to bifocal glasses. In three cases, anyone could have predicted trouble. I could now, with experience, prevent trouble in the fourth. The first failure was that of a woman store manager, aged 49, who came from 100 miles (160.9 km.) away. Her glasses were sent by mail and were never set high enough. She could not use the lower segment at all. Whereas most people would have consented to adjustment of the glasses position, she insisted on changing to bifocals without trying trifocals. In the next case, a 50-year-old otorhinolaryngologist presented a refraction problem because of high dominance and defective fusion. He was wearing — 0.75 sph. ⊃ — 0.50 cyl., axis 70, for the right eye and — 0.50 ⊃ — 0.50, axis 140, for the left eye, with an add of 1.50. He had no complaints and came in purposely to try the trifocal glasses. The old glasses provided him with 6/7.5 visual acuity in each eye at distance and apparently favored suppression of the right eye for near vision. The new prescription, — 1.00 ⊃ — 0.50, axis 75, for the right eye and — 1.00 ⊃ — 0.50, axis 140, for the left eye, gave 6/5 vision in the right eye and 6/5 + in the left eye. The new add was + 2.00.

He complained that with the new glasses, the near point (or blur point) for the right eye was 33 cm., while that for the left eye was 23 cm. The lens for the left eye was therefore changed to $-0.75 \bigcirc -0.50$, axis 140 with $+1.50$ add. This equalized the near points but caused discomfort. His visual acuity and his visual angles were satisfactory through all portions of the lenses, and there was no induced heterophoria. Possibly the trifocals encouraged fusion for near, which he did not tolerate for daily endoscopic work.

The third failure was that of a menopausal housewife, aged 46, who was disturbed that her new glasses caused the world to tilt. The prescription was $-0.25 \bigcirc +0.50$, axis 110, for the right eye and $+0.75$ cyl., axis 75, for the left eye, with an add of $+2.00$. Although she had been forewarned, she blamed the distortion on the trifocals. She was given bifocals, which caused the same distortion. This disappeared as we had promised, but she refused to take back the trifocals.

The final patient was a minister, aged 41. Ministers may be difficult to please, but I had found that they had frequently benefited by trifocals in the past. This man had been wearing $+2.00$ for the right eye and $+2.50$ for the left eye, with an add of $+1.50$. His trifocals were $+2.75 \bigcirc -0.12$, axis 180, for the right eye and $+3.50 \bigcirc -0.25$, axis 180, for the left eye, with an add of $+1.75$. His premature presbyopia was partly latent hypermetropia, for with the old glasses there was esophoria which disappeared with the new prescription. He complained of discomfort from the time he received the trifocals, in November, 1950, until he received bifocals, in July, 1951.

Part of his trouble originated in lenses set 4 mm. wider than his interpupillary distance. Plus lenses feel better when decentered in than out in most cases. However, his chief complaint was that the intermediate segment (6 mm. in height) was too narrow and that it was too hard to locate the small intermediate field. His pupillary diameter was 4.5 mm. in distance vision, so that the likely cause of a small field was his 16 mm. vertex distance. The usual distance between cornea and rear glass surface is 9 to 12 mm. This excess should have been noticed on his old glasses and his trifocal glasses made with a correspondingly larger segment area. Several patients in this series complained that the intermediate area with a 6 mm. segment was too small; so I now restrict this size segment to persons with small pupils and small vertex distances.

Five other patients would perhaps have preferred bifocals but did not go to the trouble to change back. A housewife, aged 52, was confused by the blurred diplopia of print seen through segment borders, which seemed always to be right where she looked. This, of course, is observed by all wearers of multifocal lenses at first and disappears with habitual avoidance of this level of gaze. A college professor obtained only slight improvement with a considerably different new prescription, which introduced high-powered oblique cylinders, correction for aniseikonia, and some vertical prism. He believed that his intermediate add might be the cause of some of his trouble. A divorced woman, aged 49, had always been made dizzy by glasses. She wore her trifocals for near work only and had to take them off in work with moving objects, such as her sewing machine. However, in several similar cases surprisingly favorable results were obtained. A clerk,

aged 48, had his trifocals put into old rimless frames, which were too weak to stay in place. He was never fully able to understand that he should look through any particular part of his lenses to see at a certain distance. In a final case, that of a traveling salesman with bilateral incipient cataracts, whose best visual acuity was 6/12 in the right eye and 6/20 in the left eye, bifocals would have been as helpful as trifocals.

Six other patients were pleased with the trifocals but did not think they were worth $6 more than bifocals if they had to pay for them. These patients included three housewives; a picture theater owner; a physician with myopia, who habitually went without glasses for both distance and near vision, and a monocular real estate salesman, aged 48, who likewise wore glasses only occasionally.

Of the 50 patients, 23 reported back as highly pleased and are not likely to return to bifocals. These included 11 housewives, 3 secretaries, 3 accountants, 1 physician, 1 chiropractor, 1 Y. M. C. A. executive, 1 bacteriologist, 1 orthoptist, and 1 university professor. The final 12 patients have not yet reported to me, but it is reasonable to think that they would in case of complaint because of the promise of free glasses. Those not reporting were two nurses, one secretary, one tavern owner, one arthritic patient, one physician, one farmer, one housewife, one janitor, one bookkeeper, one minister, and one dentist.

Eight patients had bifocal glasses of the same prescription for distance and near as their trifocals, and all preferred trifocals. A housewife, aged 60, whom I particularly wanted to please, got bifocals in attractive frames, which she planned to wear most of the time, while the trifocals were put in her old frames to be worn at home. The trifocals were so much better that she never wore bifocals again. Of 16 housewives in this series, 1 changed back to bifocals, and 1 had temporary complaint of blurring across segment borders, but 14 reported back enthusiastic approval.

One physician was crippled, and certain postures were difficult for him. This apparently made it impossible for him to wear bifocals all of the time, a surprising situation, since his add requirement was only + 1.25. He had tried various segments, including a 5 mm. ribbon segment, without success. The flat-top trifocal with an 8 mm. intermediate lens height has given full-time comfort for the past year. To ensure that he may never be without them, he obtained a second pair.

It is hard to understand how adds as low as +1.25 can be helpful. In this series, I prescribed a +1.50 trifocal for only one patient, but prescribed +1.25 trifocals for five patients out of curiosity about this group. Of the five patients, two would be quite unwilling to go back to bifocals. The other three would be equally pleased with bifocals but have not taken the trouble to get their glasses changed. The latter use the +0.62 intermediate add more than they do the +1.25 D. segment, so that the 8 mm. intermediate segment height used in all cases was necessary to provide for projection large enough for near use.

The two patients who were especially enthusiastic about their +1.25 trifocals were the physician, aged 45, and a woman secretary, aged 46. Unlike the other three, their vision through the near segment was blurred beyond a distance of 41 cm., whereas their near point of accommodation without an add was 62 cm. Three patients in the +1.25 group required an intermediate add for clear vision at a distance between about 45 and 60 cm.

COMMENT

If +1.25 trifocals are useful at all, it must be for persons whose interests and occupations require prolonged use of the eyes at every working distance, and who have not the accommodative range allowing sufficient reserve strength. Trifocals should be prescribed with the same reluctance that we give +0.50 reading glasses to emmetropic medical students. The only other excuse for trifocals in this power might be to make the same pair of lenses last through several years while presbyopia is developing. It would seem better in most cases to prescribe a +0.75 add until a +1.50 trifocal is indicated.

Just because a presbyope may have momentary clear vision without an add at a distance of 50 cm. does not mean he can read comfortably for prolonged periods at this distance. The relation of the amplitude of accommodation to the add required and the accommodation "left in reserve" will be discussed in a later paper.

All but one of the patients in this series received the flat-top type of trifocals. An accountant whose work required an unusually large visual angle through the segments received the ultex® A, or "onepiece trifocal. Although these "onepiece" trifocals may have a greater area of confusion at the segment borders, owing to more prismatic difference on either side, they do apparently give a larger visual field. Theoretically, the fused flat-top segment should be superior, except possibly in thick lenses, in which chromatic aberration and dispersion may be exaggerated. In the present series of 49 patients, not one complained that the reading segment gave too small a visual field. It is likely that the advantage of clear vision on the sides of the segment for use in watching the feet on steps and irregular ground would outweigh reading advantages of larger segments in most cases.

It has been advised not to change a patient from a round-top to a flat-top segment. This would raise the habitual level to which a patient drops his visual lines while reading. The visual lines are several degrees lower in round-top lenses, so that in trifocals, in which the intermediate segment is interposed, it is little change to look through a slightly lower flat-top segment. There was no complaint from this source by the many patients in this series who had been wearing round-top segments. The upper 2 mm. of a round-top segment is inefficiently used in reading and is useless in distance vision; so it should be eliminated. (My use of the term "flat-top segments" is relative and does not exclude types slightly curved.)

The most important factor in the size of the zone of confusion seen through the segment borders is the diameter of the pupil. When an image falls in perfect focus on the retina, the size and shape of the pupil can affect only its intensity. In blurred imagery, such as the view through the distance lens when one is looking at a near object, or the view through the segment when one is looking at a distant object, retinal blur circles are directly proportional to the size of the pupil. If the pupil is twice the diameter, the blur circles on the retina are twice as large. When a presbyope looks at book print directly through the segment border, he sees a zone of blurring and doubling which may include, say, six lines of print. If the print is then highly illuminated, so that the pupil constricts, this zone of blurring and doubling becomes gratifyingly less. This does not mean that the presbyope who habitually avoids segment borders, and likes to sit in a dark corner to read, should be put under bright light.

It is important that the useful area of a multifocal segment is roughly that which remains when one pupil diameter is marked out all around the edges of the segment. In other words, for a segment to be useful, it must be at least 2 mm. greater in diameter than the pupil. A segment must be 12.5 mm. plus a pupil diameter in width, in order for a person to be able to read a typewritten letter without moving his head. Ordinary flat-top trifocal lenses are from 22 to 24 mm. wide.

Only three of the patients in this series had heterophoria greater than normal. One patient with 8 Δ of exophoria at distance had 10 Δ through the reading segment. He had both bifocal and trifocal glasses of the same prescription and greatly preferred the trifocals. A woman secretary, aged 46, had both bifocals and trifocals of the same prescription with +1.25 add for near. She much preferred the trifocals because she used almost exclusively the 8 mm. intermediate segment, through which she could fuse her 8 Δ of exophoria. She had little convergence power, and the 16 Δ of exophoria through her +1.25 add could not be fused.

One should expect greater tolerance of heterophoria with trifocals because whatever divergence effect the add has in changing from distance to near vision is divided into two steps. Fusional amplitudes are higher when measured with the Risley variable prism that when measured with loose prisms.

To understand what presbyopes overcome when they wear bifocals, it is helpful to consider that anyone, whether presbyopic or not, can accept a +2.25 add. This is necessary to the success of the old-fashioned hand stereoscope. The reason that most people can relax their accommodation to this degree at such a near working distance is that enough base-in prism has been introduced to take the place of the convergence reflexly associated with this amount of accommodation. All bifocals eliminate some accommodative effort, and therefore reduce that part of convergence due to the accommodation-convergence reflex. This deficit must be made up by fusional convergence. Any distress or difficulty in wearing new bifocal glasses may be due to low fusional amplitudes, which can be improved by exercise. Since fusional amplitudes are higher when deviations of vergence are presented in smaller steps, trifocals should be easier to wear from the first.

If there is any trick in prescribing trifocals, it is in having a trifocal-bifocal trial set for demonstration to the patient. People are not prejudiced against trifocals but suspect ideas they do not fully understand. In the fitting of trifocals, the presence of an intermediate area should not change the level of the top of the reading segment. However, it is more certain that the intermediate area will not offend the patient in distance gaze if the glasses are fitted slightly low for the first week. The nose pads and lens tilt can then be adjusted to the most efficient level, not to intrude too much in distance gaze in common erect posture.

The routine practice of underestimating the +0.25 add can be discontinued in trifocals. This was done to favor vision at the intermediate distance. Routine underestimation for the first bifocals, or for bifocals to be worn part time, has also been common, and can be discontinued.

I have had good results in prescribing trifocal glasses for aphakic patients with good acuity. There is a large amount of chromatic aberration and astigmatism of oblique pencils to be overcome, and the lenses should therefore be as thin as possible and of high-quality manufacture.

Presbyopic patients may complain that when they look at a distant object it takes too much time for vision to clear. It takes even more time for them to read well after distance gaze. Patients will say, "Give me time; then I'll see it." Lancaster and Williams,[4] in their studies of accommodative fatigue, found that the amplitude of accommodation was increased, not decreased as expected, after prolonged near work. Robertson [5] studied this delay in reaching an accommodative level and concluded that it not only caused inefficient vision but produced discomfort. If an appropriate add could be supplied in glasses for every possible distance of gaze, accommodation would not be necessary, and clear vision would be instantaneous. Trifocals represent a step in this direction. It may be that patients who have never learned to wear bifocal glasses avoid them because of this delay in clear vision in a quick shift from distance to near. A similar shift of gaze with removal of single-vision reading glasses would allow time in which this delay would be less noticeable.

I believe that it is a mistake to prescribe trifocal glasses without demonstrating the use of the three lenses. Some advertising might lead one to believe the lenses are so perfectly designed that the patient need not be told the lenses are trifocal. Patients must learn the use of the three lenses and develop habits for use of the appropriate lens for the distance involved. Vision through a segment border must be avoided automatically, or the patient will suffer blurring and diplopia. Only if he understands the limitations of trifocal glasses will he be satisfied. Trifocals do not really restore youthful vision.

SUMMARY AND CONCLUSIONS

Trifocals were made available at the price of bifocals to all my presbyopic patients during the past year with the guarantee that if not satisfactory they would be replaced by bifocals free of charge. The results for 50 patients who would not otherwise have worn trifocals are reported.

Many presbyopes of all occupational groups desire trifocal glasses but do not know they exist. Most presbyopes should have trifocal lenses demonstrated to them during a routine refraction. No additional time or explanation is necessary if a trial lens set of trifocals is used. Of 16 housewives in this series, 14 were highly enthusiastic about their trifocals. For only 4 of the entire 50 patients may use of trifocals be said to have been unsuccessful. Three of these promised trouble during the refraction, and the fourth had trouble which could have been prevented.

Trifocals with an add of only +1.25 for near proved better than bifocals in two of five cases, for the reasons discussed.

The intermediate segment should be 7 or 8 mm. in height except for those patients who have small pupils and short eye-to-glass distances. The segment should be set slightly low for the first week, then elevated as high as tolerated.

Trifocal lenses are contraindicated for patients with poor visual acuity and for persons who use glasses infrequently. They are particularly helpful for monocular patients or for those with amblyopia ex anopsia.

4. Lancaster, W. B., and Williams, E. R.: New Light on the Theory of Accommodation with Practical Applications, Tr. Am. Acad. Ophth. 1914, pp. 170-195.

5. Robertson, C. J.: Measurement of Speed of Adjustment of Eyes to Near and Far Vision, Arch. Ophth. **15**:423-434 (March) 1936.

ADRENERGIC BLOCKING AGENTS IN TREATMENT OF GLAUCOMA

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REPORTS[1] demonstrating the tension-lowering possibilities of adrenergic blocking agents in glaucoma are occurring in the literature. There are several types of adrenergic blocking agents. These were tested on a number of glaucomatous eyes at the Wills Hospital to determine their relative efficacy and to clarify, if possible, the type or types of glaucoma in which these agents might be most useful.

Adrenergic blocking agents may be defined, according to Nickerson,[2] as agents which inhibit certain responses of effector cells to epinephrine, related amines, and sympathetic nerve impulses. This action of adrenergic blocking agents is distinct from the action of substances which can prevent a sympathicoadrenal discharge by block of nerve impulses in ganglia, such as tetraethylammonium effects, or along peripheral neurons, such as local anesthetics produce, or in the central nervous system, such as barbiturates and other central nervous system depressants bring about.

Since these compounds do not lyse the nerve endings, the mediator, or the effector cell, it does not seem that the term "sympatholytic" or "adrenolytic" is satisfactory. Therefore the term "adrenergic blocking agent" has been used.[2]

There are many types of adrenergic blocking agents, examples of which are listed in the following tabulation.

β-halo-alkylamines, e. g., dibenamine®
Imidazolines, e. g., benzazoline (priscol®)
Benzodioxans, e. g., piperidylmethyl benzodioxane (933F) and piperoxan (benodaine®)
Ergot alkaloids, e. g., dihydroergocornine (DHO180)
Yohimbins, e. g., yohimbin; ethyl yohimbin

An example of an adrenergic blocking agent is dibenamine® (N-N-dibenzyl-β-chloroethylamine), which is a type of β-halo-alkylamine, one of the most recently discovered series of adrenergic blocking agents. It has received most attention in ophthalmology. This agent will block the mydriasis that occurs in cats when placed

From the Research and Clinical Departments, Wills Hospital.

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The dibenamine® hydrochloride was supplied by Smith, Kline & French Laboratories. Benodaine® hydrochloride was supplied by Merck & Company, Inc. Dihydroergocornine is a product of Sandoz Pharmaceuticals.

1. (*a*) Thiel, R.: Experimental and Clinical Investigations on the Influence of Ergotamine (Gynergen) on the Intraocular Pressure in Glaucoma, Klin. Monatsbl. Augenh. **77**:753, 1926. (*b*) Christensen, L., and Swan, K. C.: Adrenergic Blocking Agents in the Treatment of Glaucoma, Tr. Am. Acad. Ophth. **53**:489, 1949. (*c*) Posner, A.: Effect of Certain Hydrogenated Alkaloids of Ergot on Glaucoma, Am. J. Ophth. **33**:1551, 1950. (*d*) Bloomfield, S., and Haimovici, H.: Effect of Dibenamine in Chronic Simple Glaucoma, Arch. Ophth. **43**:969 (June) 1950. (*e*) Newell, F. W.; Ridgeway, W. L., and Zeller, R. W.: Treatment of Glaucoma with Dibenamine, Am. J. Ophth. **34**:527, 1951. (*f*) Clark, W. B., and Duggan, J. W.: Use of Dibenamine in Treatment of Acute Congestive Glaucoma, ibid. **34**:535, 1951.

2. Nickerson, M.: Pharmacology of Adrenergic Blockade, J. Pharmacol. & Exper. Therap. **95**:27, 1949.

in dim illumination and will block the response to cervical sympathetic stimulation. In man, a dibenamine®-induced miosis is more pronounced than in experimental animals, probably because of the larger sympathetic component that controls the iris of man. Dibenamine® is derived from, and related to, the nitrogen mustards (methyl-*bis* or *tris* [β-chloroethyl]-amine), and it is rather toxic when injected subcutaneously or intraperitoneally. This drug does not alter or destroy epinephrine. It does not inhibit the release of sympathin E and does not significantly alter the response of sympathetic nerves to electrical or reflex activity.[2]

A brief word about ergot preparations is in order. Stoll and Hofman,[2a] in 1943, showed that ergotoxine is not a single chemical substance but a mixture of three alkaloids: ergocornine, ergocristine, and ergocryptine. All these ergot alkaloids contain lysergic acid as a characteristic constituent. Stoll and Hofman showed that one double bond of lysergic acid can be easily hydrogenated, yielding new chemical substances, with definite chemical and pharmacological properties. These new hydrogenated alkaloids have been shown to be less toxic and stronger in adrenergic blocking.

TABLE 1.—*Effect of Adrenergic Blocking Agents in Chronic Primary (Wide-Angle) Glaucoma*

Case No.	Eye	Stage of Glaucoma	Initial Tension, Mm. Hg (Schiøtz)	Benodaine® *	DHO180 †	Dibenamine®
13	O.D.	Far advanced	39	No effect	No effect	No effect
	O.S.	Far advanced	36	No effect	No effect	No effect
14	O.D.	Moderately advanced	36	No effect	.....	No effect
	O.S.	Moderately advanced	42	No effect	.....	No effect
15	O.D.	Far advanced	42	No effect	.....	3 mm. drop
	O.S.	Moderately advanced	30	No effect	.....	No effect
16	O.D.	Early	39	No effect	No effect	10 mm. drop
	O.S.	Moderately advanced	33	No effect	No effect	No effect

* Piperoxan.
† Dihydroergocornine.

Various hydrogenated ergot alkaloids have been prepared. Examples are dihydroergotamine, also called DHE45; dihydroergocornine, or DHO180; dihydroergocristine, and dihydroergocryptine.

Benzodioxans appear to be effective primarily against responses to circulating sympathomimetic agents and to sympathetic nerve activity. The adrenergic blockade produced by benzodioxan is rather weak and is readily overcome by large doses of epinephrine. Benzodioxans are capable also of directly stimulating smooth muscle of many types.

PRESENT INVESTIGATION

Method.—All patients chosen for studies had either primary or secondary glaucoma that had not been responding to the previously employed therapy. All forms of therapy were discontinued 6 to 12 hours prior to trial with adrenergic drugs.

Dibenamine® was given intravenously in doses of 4 to 5 mg. per kilogram of body weight in 500 cc. of sodium chloride solution over periods of one and one-half hours. Piperoxan (benodaine®) was administered similarly. Dihydroergocornine was given as 1 mg. intravenously. In the following tabulation are listed side-reactions that may occur with this therapy.

Tachycardia	Substernal pressure
Hyperpnea	Precordial distress
Headache	Nausea
Fright	Vomiting
Dizziness	Local tissue pain and necrosis and venous thromboses
Sighing respirations	Central nervous system excitation

2a. Stoll, A., and Hofman, A.: Die Alkaloide der Ergotoxin Gruppe Ergocristin, Ergokryptin und Ergocornin, Helvet. chim. acta **26**:1570, 1943.

TABLE 2.—*Effect of Adrenergic Blocking Agents in Acute (Narrow-Angle) Glaucoma*

Case No.	Eye	Duration of Glaucoma, Hr.	Initial Tension, Mm. Hg (Schiøtz)	DHO180	Dibenamine®
6	O.D.	16	52	10 mm. drop	.....
7	O.S.	8	35	No effect	.....
8	O.D.	16	39	.....	6 mm. drop
9	O.D.	24	33	.....	3 mm. drop
10	O.S.	18	46	6 mm. drop	.....
11	O.S.	36	33	.....	No effect
12	O.D.	48	65	.....	30 mm. drop

TABLE 3.—*Effect of Adrenergic Blocking Agents in Chronic Primary (Narrow-Angle) Glaucoma*

Case No.	Eye	Stage of Glaucoma	Initial Tension, Mm. Hg (Schiøtz)	Benodaine®	DHO180	Dibenamine®
1	O.D.	Far advanced	39	No effect	3 mm. drop	3 mm. drop
	O.S.	Far advanced	42	No effect	3 mm. drop	No effect
2	O.D.	Moderately advanced	42	No effect	.....	No effect
	O.S.	Far advanced	36	No effect	.....	No effect
3	O.D.	Early	45	No effect	4 mm. drop	9 mm. drop
	O.S.	Moderately advanced	33	No effect	No effect	No effect
4	O.D.	Moderately advanced	39	No effect	.....	No effect
	O.S.	Far advanced	42	No effect	.....	No effect
5	O.D.	Far advanced	48	No effect	.....	6 mm. drop
	O.S.	Early	42	No effect	.....	9 mm. drop

TABLE 4.—*Effect of Adrenergic Blocking Agents in Secondary Glaucoma*

Case No.	Eye	Type of Uveitis	Initial Tension, Mm. Hg (Schiøtz)	Benodaine®	DHO180	Dibenamine®
16	O.D.	Traumatic	58	No effect	.....	5 mm. drop
17	O.S.	Nonspecific	35	No effect	.....	No effect
18	O.S.	Nonspecific	35	No effect	No effect	No effect
19	O.D.	Tuberculous (?)	39	No effect	.....	No effect
20	O.D.	Nonspecific	60	No effect	.....	15 mm. drop
21	O.D.	Brucella (?)	56	No effect	6 mm. drop	12 mm. drop
22	O.D.	Nonspecific	33	No effect	.....	No effect
23	O.S.	Nonspecific	52	8 mm. drop	.....	.....
24	O.D.	Nonspecific	40	No effect	No effect	No effect
25	O.S.	Nonspecific	38	No effect	No effect	No effect
26	O.S.	Nonspecific	55	No effect	.....	20 mm. drop
			Ectopia Lentis			
27	O.D.	.....	48	No effect	.....	No effect
28	O.D.	.....	30	No effect	.....	No effect
			Aphakia			
29	O.S.	.....	40	No effect	No effect	No effect

TABLE 5.—*Summary of Results with Adrenergic Blocking Agents*

Type of Glaucoma	No. of Eyes	Benodaine®*	DHO180*	Dibenamine®*
Chronic (narrow-angle)	10	0/10	0/4	3/10
Acute glaucoma	7	...	2/3	2/4
Chronic (wide-angle)	8	0/8	0/4	1/8
Hypertensive uveitis	11	1/11	1/5	4/10
Ectopia lentis	2	0/2	...	0/2
Aphakia glaucoma	1	0/1	...	...
Total	39	1/32	3/16	10/34

* The numerator indicates the number of eyes showing improvement—with a fall of pressure greater than 5 mm. Hg (Schiøtz); the denominator, the number of eyes treated.

Results.—It is evident from this tabulation and Tables 1, 2, and 3 that piperoxan in the dose employed failed to lower the intraocular pressure significantly in glaucomatous eyes. The hydrogenated alkaloid dihydroergocornine and dibenamine® were more successful.

COMMENT

According to Nickerson,[2] dibenamine® is the most potent adrenergic blocking agent of the three, and piperoxan, the benzodioxan compound, the least potent. Dibenamine® makes a resistant block to epinephrine, whereas piperoxan can easily be overcome by epinephrine.

These results confirm those of earlier investigators [1] in that they show a tension-lowering response of glaucomatous eyes to adrenergic blocking agents. The results, however, were not as widely successful as those of others in the treatment of acute glaucoma and hypertensive uveitis. The effects in chronic glaucoma observed in the present series were very slight.

Posner [1c] reported no benefit in chronic glaucoma with the hydrogenated alkaloids, and Bloomfield and Haimovici found an effect with dibenamine.® However, the disease in Bloomfield's cases was mild and had already been controlled by other measures before dibenamine® was tried. In all the cases in the present series the glaucoma had been uncontrolled by therapy previously employed.

In no eye did the pressure-lowering effect last longer than 48 hours. Therapy was not repeated with these agents in any successful case.

It is evident from a study of the tables that the most precipitous falls in intraocular pressure occurred in eyes with initial pressures above 50 mm. Hg (Schiøtz). This suggests that the adrenergic blocking agents are more effective at the higher pressure levels.

The intraocular tension-lowering mechanism of the adrenergic blocking agent is not known, and the possibilities have been adequately discussed elsewhere.[3] The present data simply illustrate that of the three adrenergic blocking agents, dibenamine® and (dihydroergocornine) were successful in lowering intraocular pressure in glaucomatous eyes. Also, the greatest benefit occurred in those eyes with narrow-angle glaucoma and with hypertensive uveitis.

SUMMARY

1. Adrenergic blocking agents lowered intraocular pressure in some glaucomatous eyes that had failed to respond to other medical and/or surgical therapy.

2. Piperoxan (benodaine®) was the least effective of the three agents tried.

3. Narrow-angle glaucoma and hypertensive uveitis responded to adrenergic agents more than chronic wide-angle glaucoma in this series.

4. The most pronounced fall in intraocular pressure occurred in eyes with pressures above 50 mm. Hg (Schiøtz) prior to onset of therapy, although a moderate decrease was noted in some eyes with lower initial pressures.

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3. Christensen and Swan.[1b] Posner.[1c] Bloomfield and Haimovici.[1d] Newell, Ridgeway, and Zeller.[1e] Clark and Duggan.[1f] DeLong, S., Jr., and Scheie, H. G.: Action of Dibenamine on Ocular Structures—Clinical and Experimental Studies, presented at a meeting of the College of Physicians of Philadelphia, Section on Ophthalmology, April 19, 1951.

UNILATERAL PROPTOSIS DUE TO FIBROUS DYSPLASIA OF BONE

Report of Two Cases

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THE DIAGNOSIS and management of unilateral proptosis have been reported by Ellett,[1] Pfeiffer,[2] Thacker,[3] Massoud,[4] and Savin.[5] Fibrous dysplasia of bone giving rise to proptosis has rarely been mentioned in such reviews. Two such cases are described. Savin (liontiasis ossei); Pfeiffer (osteitis fibrosa cystica); Proffitt, McSwain, and Kalmon;[6] Pugh,[7] Sosman,[8] and Schlumberger[9] have mentioned this possibility in reporting cases of exophthalmos. In these instances the lesion was usually diffiuse, involving extensive portions of the frontal bone, orbit, and paranasal sinuses. Yet the process may be quite discrete (Sosman) in the supraorbital plate and amenable to surgical excision. The surgical treatment in such cases has had little consideration.

Fibrous dysplasia of bone is still a comparatively uncommon entity, and extensive reports of such lesions are few. Case series with reviews of the literature, x-ray findings, clinical manifestations, and surgical management have recently been compiled by Proffitt and associates,[6] Schlumberger,[9] and Schlesinger, Keats and Ruoff.[10] Pathological characteristics of the process have been dealt with most

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1. Ellett, E. C.: Unilateral Exophthalmos, J. A. M. A. **116**:1-7 (Jan. 4) 1941.

2. Pfeiffer, R. L.: Roentgenography and Exophthalmos with Notes on the Roentgen Ray in Ophthalmology, Am. J. Ophth. **26**:724 (July); 816 (Aug.), and 928 (Sept.) 1943.

3. Thacker, E. A.: Orbital Proptosis, Illinois M. J. **88**:246-252 (Nov.) 1945.

4. Massoud, F.: Proptosis—Differential Diagnosis, Brit. J. Ophth. **30**:622-630 (Oct.) 1946.

5. Savin, L. H.: Proptosis: Its Differential Diagnosis and Treatment, M. Press **220**:335-338 (Oct. 27) 1948.

6. Proffitt, J. N.; McSwain, B., and Kalmon, E. H., Jr.: Fibrous Dysplasia of Bone, Ann. Surg. **130**:881-893 (Nov.) 1949.

7. Pugh, D. G.: Fibrous Dysplasia of the Skull: A Probable Explanation for Leontiasis Ossea, Radiology **44**:548-555 (June) 1945.

8. Sosman, M. C., in discussion on paper by Pugh.[7]

9. Schlumberger, H. G.: Fibrous Dysplasia of Single Bones (Monostotic Fibrous Dysplasia), Mil. Surg. **99**:504-527 (Nov.) 1946.

10. Schlesinger, P. T.; Keats, S., and Ruoff, A. C., III: Fibrous Dysplasia, J. Bone & Joint Surg. **31-A**:187 (Jan.) 1949.

extensively by Lichtenstein and Jaffe;[11] Valls, Polak, and Schajowiez,[12] and Schlumberger.[9] The etiology remains obscure. In the polyostotic form there may be a primary metabolic or growth disorder, which at times is associated with evidence of parathyroid dysfunction. The role of trauma in the monostotic form is debatable, but since the histological picture may closely resemble "final cicatricial stages and processes rather than . . . dysplastic stages" (Valls and associates), this additional possibility has been considered.

Delaney[13] has discussed the use of testosterone in the management of an inoperable lesion with recurrence, but the rationale of this therapy is not clear. Sosman recommends consideration of x-ray therapy in small doses (750 to 800 r).

In each of the two cases reported here the primary sign on referral was unilateral proptosis of long standing. In each instance the lesion was apparently amenable to surgical removal and the orbit was decompressed.

REPORT OF CASES

CASE 1.—A white man aged 21 was transferred to Walter Reed General Hospital on Dec. 21, 1949, with a diagnosis of arterial aneurysm on the left, probably congenital, of the ophthalmic artery. Two weeks prior to hospitalization the patient had reported to sick call with a sprained thumb. At that time the physician noted that his left eye protruded slightly more than the right. On Oct. 13, a roentgenogram of the left orbit was reported to have shown an oval area of bone destruction, about 5 cm. in diameter, overlying the roof of the left orbit. It was thought to represent an epidermoid or a mucocele. On Nov. 15, therefore, the patient underwent a craniotomy. The following description is taken from the operative note.

There was unusual vascularity in all layers of the incision—skin, muscle, bone, and dura. Bleeding was brisk and controlled with difficulty. The dura was opened, exposing "abnormal vascularity of the cortical vessels, with large venous channels extending down over the frontal pole . . ." The lesion in the roof of the orbit "was about the size of a golf ball and protruded directly upward from the roof of the orbit. There were innumerable vessels, arterial and venous, in the dura of the floor of the frontal fossa overlying the lesion." Dissection in the surrounding periosteum was associated with "excessive arterial bleeding." Arterial blood was obtained from a No. 19 needle, which was introduced into the lesion in two places. It was "apparent that the blood supply of this lesion entered through the roof of the orbit . . . at a point not accessible at this time." Bleeding was controlled and the incision closed, in the anticipation of doing an arteriographic study of the external and internal carotid vessels at a later date . . . to determine where the blood supply to the aneurysm came from. The patient had a convulsion with postictal weakness on the right side one week after operation, and an epidural hematoma was evacuated at that time. His postoperative course was otherwise uneventful.

On his admission to the neurosurgical section of Walter Reed General Hospital, the physical examination showed nothing remarkable except that the left pupil was slightly dilated and the left eye was more protuberant than the right. He had a well-healed coronal skin incision.

On Jan. 7, 1950, arteriograms of the left internal and external carotid vessels were performed, and no evidence of vascular anomaly was demonstrated. As a precautionary measure prior to craniotomy, the left external carotid artery was ligated. On Jan. 27, a left frontal craniotomy was performed (Dr. Hugo V. Rizzoli) through the previous bone flap, and the tumor mass was approached extradurally, since no evidence of vascular anomaly could be demonstrated in arteriograms. There was a distinct dome-shaped area in the supraorbital plate, approximately 2.5 cm. in diameter. The summit of this bone was very thin and was removed with a small curette.

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11. Lichtenstein, L., and Jaffe, H. L.: Fibrous Dysplasia of Bone, Arch. Path. **33**:777-816 (June) 1942.

12. Valls, J.; Polak, M., and Schajowiez, F.: Fibrous Dysplasia of Bone, J. Bone & Joint Surg. **32-A**:311-322 (April) 1950.

13. Delaney, A. J.: Monostotic Fibrous Dysplasia of the Skull: Report of a Case, U. S. Armed Forces M. J. **1**:1323-1328 (Nov.) 1950.

Within, there was a firm-walled cyst, from which was evacuated about 8 cc. of darkly xanthochromic but clear fluid. Cultures of this fluid showed no growth of bacteria or fungi. The cyst was removed *in toto* and measured approximately 2 cm. in diameter. The remainder of the space within the supraorbital plate was filled with soft, yellowish, rather firm, loculated material, which was removed with curette and rongeurs. The inner table of the supraorbital ridge was intact, but very thin, and was therefore removed from the underlying capsule in order to decompress the contents of the orbit. The patient's postoperative course was uneventful, and four weeks after operation there was some improvement in the proptosis, which continued to recede until he was returned to duty.

Pathological Report of Specimen (Major James L. Hansen).—Gross Examination: A. The specimen, of bone overlying the tumor, consists of several fragments of cancellous bone. One surface is grayish-brown and smooth; the other is rough and corrugated and contains clotted blood and small fragments. B. The specimen consists of a cyst-like structure, 2.5 cm. in diameter, which grossly appears to contain solid material, in addition to fluid. To one surface of this structure is appended a flat, plaque-like area, the surface of which is smoothly corrugated and measures 2 cm. in diameter. The surface of the rest of the cyst is rough and granular, contains a number of small blood vessels, and is yellowish. Upon section, a bloody fluid escapes, revealing

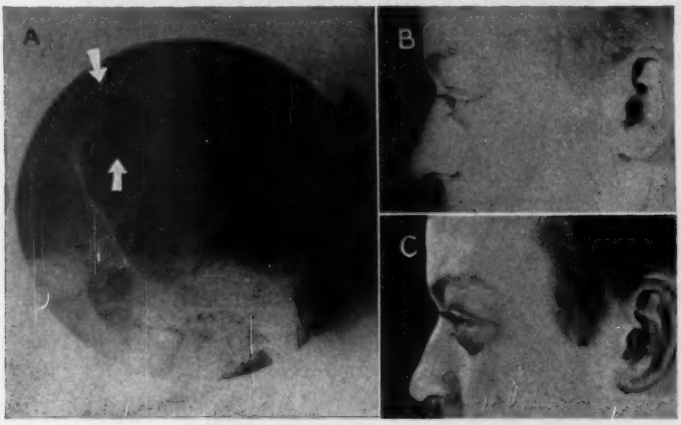

Fig. 1 (Case 1).—*A*, roentgenogram of supraorbital lesion before decompression; *B*, proptosis before orbital decompression; *C*, proptosis four months after orbital decompression.

a smooth cyst wall, to areas of which are attached trabeculae of grayish-brown tissue. The portion of the cyst wall underlying the plaque previously mentioned is thicker than the rest, but the general architecture of the cyst wall appears more uniform. C. The specimen, labeled tumor mass, consists of a large number of fragments of tissue, granulomatous in character, with areas of old and recent hemorrhage and a grayish-white fibrinous capsule, which is friable and fleshy.

Microscopic Study: A. The small fragment of bone shows compact cancellous bone with considerable increase in the number of bony trabeculae. Very little marrow space is present. The marrow shows no myeloid structure. It contains some blood. Numerous osteoblasts line many of the sinusoids against the numerous small, thin bone trabeculae. One surface of the bony fragment shows aseptic necrosis of bone. The periosteum is not remarkable. B. What appears to be the wall of a bone cyst is composed of dense fibrous tissue, containing numerous small fragments of degenerated bone. The tissues show a pronounced reaction. Large giant cells are present. These are of the type that is often associated with bony lesions and cysts of bone. Though xanthomatous cells are apparent, there appear to be no hemosiderins scattered through the cyst wall. The entire central core of tissue has a hyaline appearance, and through this

numerous small fibroblasts and capillaries are seen. The primary component of this bone tumor is connective tissue, which is fairly well vascularized and is frequently arranged in interrelating bundles and whorls. Within the connective tissue, and most abundant at its periphery, are trabeculae of partly calcified and poorly organized bone. Some of the incarcerated connective tissue cells are indistinguishable from osteocytes. Several pseudogiant cells are apparent.

The diagnosis is that of fibrous dysplasia of bone.

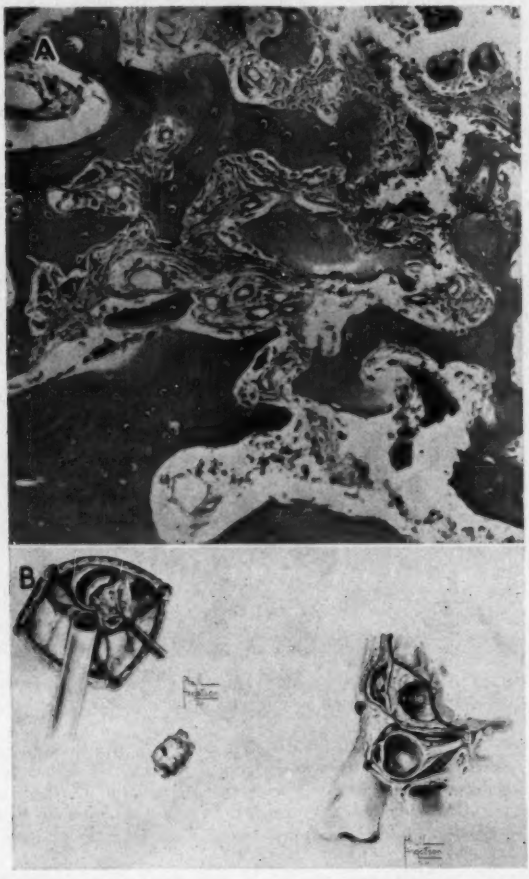

Fig. 2 (Case 1).—*A*, characteristic appearance of fibrous dysplasia with fibrous and osteoid tissue (hematoxylin-eosin stain; × 110); *B*, drawing showing removal of the cyst wall and reconstruction of the lesion in cross section.

Case 2.—A white man, aged 27, was admitted to Walter Reed General Hospital on June 1, 1950, because of proptosis of the right eye. He was said to have been born with the left eye higher than the right. Vision in the left eye had always been much poorer than that in the right eye. In December, 1948, visual acuity was 20/15 in the right eye and 20/40 in left eye. He was

struck between the eyes by a baseball in March, 1949, with no loss of consciousness. Seven months prior to admission he noted progressively decreasing visual acuity on the left side but had no headaches or diplopia.

His past history was not remarkable except for diphtheria at the age of 7 years and tonsillectomy at the age of 12. The medical records state that he was hospitalized in 1949 for peptic ulcer.

On physical examination the inferior orbital margins appeared symmetrical. The right superior orbital margin was more prominent than the left but was not depressed. The pupil on the left failed to respond to light or in accommodation. Extraocular movements were intact, though the left eye deviated to the left with binocular vision. Visual acuity was 20/15 in the right eye and was limited on the left to light perception in the central fields. The peripheral field of the right

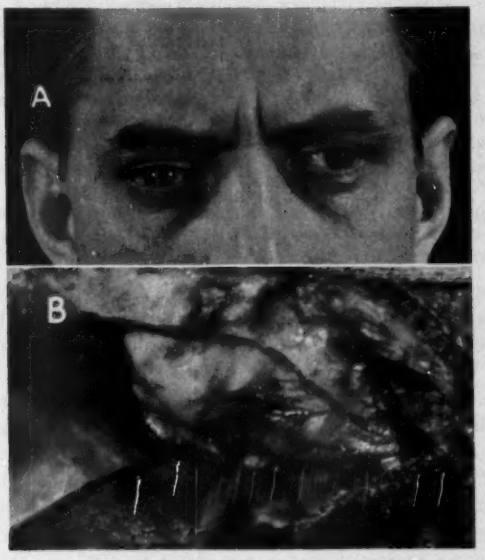

Fig. 3 (Case 2).—*A*, patient's appearance on admission, with proptosis of the right eye and divergence of the left eye; *B*, dome-shaped lesion in the supraorbital plate prior to decompression.

eye showed a 20-degree restriction in all quadrants. There was optic nerve atrophy on the left with atrophic cupping. The right optic disk appeared normal. X-ray examination showed no abnormality of the optic foramen. A discrete, cyst-like lesion in the supraorbital plate was thought to represent fibrous dysplasia. The electroencephalogram showed a basic frequency of 11 cps, with a slight asymmetry of amplitude in the temporal leads, the left side being lower than the right. The spinal fluid contained 2 cells per cubic millimeter, and 74 mg. of sugar, 720 mg. of chlorides, and 26 mg. of total protein, per 100 cc. There was no increase in globulin. The cardiolipin test gave a negative reaction for syphilis, and the colloidal gold curve was 0000000000. Routine blood cell counts, serologic tests, and urinalysis revealed nothing abnormal. No clear explanation for the optic atrophy could be found. Although it was difficult to explain the left visual defect by a lesion involving the right orbit, it was decided to decompress the right orbit and optic foramen, to correct the proptosis, and possibly to relieve tension on the optic chiasm, if such existed.

At operation, with the patient under anesthesia induced with thiopental (pentothal®) sodium and maintained with oxygen and ether, a right frontal craniotomy was performed. The dura

was stripped gently from the bone along the lateral edge of the greater wing of the sphenoid and the roof of the orbit. Immediately the lesion, measuring 2 cm., in the supraorbital plate was encountered. This prominence was entered, using a mastoid rongeur, and found to contain a white, crumbly, cheeselike material, which was easily removed with a curette. The hard bone overlying this lesion was removed by means of rongeurs, and the lower wall of the pocket was opened with a chisel and the ethmoid sinus entered. The sinus was packed off with gelfoam,* moistened with saline solution containing 100,000 units of penicillin, and the roof of the orbit was removed as widely as possible laterally, anteriorly, and posteriorly. Similar cheesy material was encountered over the anterolateral aspect of the roof of the orbit, involving a small portion of the anteromedial wall of the sphenoid ridge. The orbital foramen was opened to decompress the optic nerve. When normal bone had been encountered at all limits of the dissection, the ethmoid sinus was again examined. The mucous membrane lining of the cells was removed; the ostium of the sinus was packed with bone wax, and penicillin-impregnated gelfoam* was reinserted over this.

The postoperative course was uneventful except for the occurrence of mild, persistent right frontal headaches for approximately six weeks and a clicking noise over the right eye with rapid movement of the head. This gradually decreased in intensity, but was still present on his discharge. Visual acuity on Sept. 6, was 20/15 in the right eye and was unchanged for light and dark perception in the left eye. The visual fields had not changed. The right eye was much less prominent and was no longer depressed laterally, although for six weeks after operation it continued to appear more prominent than the left for short intervals. The patient was returned to duty on Nov. 15, 1950.

Gross examination of the tissue showed numerous irregular fragments of bone and locules of granular, yellow-gray tissue. Microscopic sections showed both osteoblastic and osteoclastic activity, with interspaced areas of fibrous and osteoid activity and irregular calcification.

In these two cases there was no area of pigmented skin or abnormal distribution of hair. Skeletal surveys showed no other lesions of bone. The calcium and phosphorus levels of the blood were within normal limits. The possibility of additional bony lesions developing in the future cannot be denied, but no evidence of the polyostatic form of this process could be found during their hospitalization. While Valls believes that polyostatic fibrous dysplasia of bone may be a developmental variant, and that the monostotic form is probably secondary to a healing process following injury, it is unlikely that such a process due to trauma could involve the supraorbital plate without a history of severe head injury.

Pfeiffer [2] reports that on the basis of the x-ray examination alone in cases of exophthalmos the correct diagnosis was made in 40% of 200 cases and was suggested in an additional 20%. Reeves, Baylin, and Moran [14] believe that the correct diagnosis can be made in about 25% of such cases on the basis of x-ray findings alone. Windholz [15] describes the x-ray findings in fibrous dysplasia —"dense bone spicules and alternating clear translucent areas of ground glass quality which are characteristic" and states the opinion that these findings will establish not only the correct, but also the differential, diagnosis. The diagnostic criteria for x-ray changes associated with dermoids in this region are well described by Thornkill and Anderson.[16] In Case 1 the lesion demonstrated roentgenologically was thought to resemble most nearly a dermoid, although the possibility of its being

14. Reeves, R. J.; Baylin, G. J., and Moran, F.: X-ray Conditions of Unilateral Exophthalmos, North Carolina M. J. **9**:66-73 (Feb.) 1948.

15. Windholz, F.: Cranial Manifestations of Fibrous Dysplasia of Bone, Am. J. Roentgenol. **58**:51-63 (July) 1947.

16. Thornkill, E. H., and Anderson, B.: Extradural Diploic Epidermoids Producing Unilateral Exophthalmos, Am. J. Ophth. **27**:477-482 (May) 1944.

fibrous dysplasia or an eosinophilic granuloma[17] also was recognized. In Case 2 the correct diagnosis was made on the basis of the initial x-ray examination.

The surgical approach to each lesion was directed toward total excision of the involved bone. While this appeared to have been achieved at operation, more time will have to elapse before final evaluation in respect to recurrence is warranted. In each instance orbital decompression was performed, but Tenon's capsule was not incised, since the source of pressure causing the proptosis was outside this structure.

SUMMARY

Two cases of long-standing unilateral proptosis due to monostotic fibrous dysplasia of bone, limited to discrete lesions of the supraorbital plate, are reported. The possibility of correct diagnosis in such a case on the basis of x-ray findings is noted, and the response to orbital decompression is described.

NOTE.—A white woman, aged 31, with progressive unilateral proptosis and increasingly severe orbital pain with a dilated right pupil has recently been treated in a fashion similar to that in the two cases reported here. Histological studies of the supraorbital plate, which was soft and ½ inch (1.3 cm.) thick, showed changes consistent with those seen in fibrous dysplasia of bone. There was no evidence of multiple lesions or metabolic disturbance in this case.

17. Maynard, Wheeler: Exophthalmos Caused by Eosinophilic Granuloma of Bone, Am. J. Ophth. **29**:980-983 (Aug.) 1946.

LOCALIZED INJECTION OF THE UPPER QUADRANT * OF THE BULBAR CONJUNCTIVA

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THE PURPOSE of this paper is to call attention to an isolated sign—congestion of the upper quadrant of the bulbar conjunctiva without other ocular involvement. Congestion of the bulbar conjunctiva is a common sign in most diseases of the anterior segment. Congestion only in one sector serves as a guide to a pathological process in the particular sector. Among such typical conditions are phlyctenular conjunctivitis and keratitis, keratitis rosacea, early interstitial keratitis and episcleritis.

I have observed a number of patients with congestion of the bulbar conjunctiva localized to the upper quadrant only. The condition did not fit any of the known ocular diseases with sector-like congestion of the bulbar conjunctiva of a local or general cause. Altogether, 20 such patients have been observed, and its incidence is estimated as 1 in 1,500 patients with ophthalmic disease. The age of the affected persons, eight men and 12 women, ranged from 21 to 68 yr. The symptoms were watering and scratchiness of the eyes, a gritty sensation, more pronounced when reading. The eyes were sensitive to bright light, dust, and wind; some patients complained of tiredness, and a burning sensation. The patients had had these symptoms from several days to one year when they were first seen. There was moderate to intense congestion of the bulbar conjunctiva from the upper fornix to the upper limbus, most pronounced between the 11 and the 1 o'clock position. The part of the bulbar conjunctiva which is visible in the palpebral opening and the part which is covered by the lower lid were normal. The vascular curtain was made up of the conjunctival vessels, the larger ones even slightly bulging from the conjunctival plane. The largest vessels ran more or less vertically, but oblique branches produced the effect of a net. Slit-lamp examination revealed a superficial and a deeper layer of vessels. The limbal arcades and their terminal loops were dilated, but no vessel entered the cornea proper, an important point in the differential diagnosis. Episcleral vessels probably contributed to the congestion in the severest cases. Only in a few cases were there congestion beyond the upper fornix and fine papillary hypertrophy at the upper edge of the tarsus, but even in these cases the lower portion of the tarsal conjunctiva was not involved. Slit-lamp examination failed to reveal a pathologic change in the cornea or uvea. In the majority of the cases there was no conjunctival secretion. In a few cases some mucous secretion

* The term "upper quadrant" as used in this paper refers to that portion of the bulbar conjunctiva which is between the 10:30 and the 1:30 meridian.

was noted in the mornings. In these cases no pathogenic bacteria were found, and it was thought that the rubbing, irritating action of the uneven bulbar conjunctiva produced the slight secretion. The condition was bilateral in all but three cases, although in several there was a difference in the intensity in the two eyes.

This disease picture was first described by me in 1944.[1] Since then five new cases have been observed, and a theory of pathogenesis has been elaborated.

Mrs. W. M., aged 46, complained that her eyes had felt strained for a month and that they burned and were irritated as the day wore on; this was worse when she was doing close work. She had moderate myopia, with correct refraction. There was no heterophoria. A typical congested vascular net was present in the upper quadrant of the bulbar conjunctiva of both eyes. Only Bacillus xerosis was obtained on culture. She had had a flare-up of rheumatic fever with cardiac involvement at the onset of the ocular trouble.

Mrs. L. W., aged 56, had watering of the left eye at night, with a foreign-body sensation. A small degree of hyperopic astigmatism was noted in each eye. The upper quadrant of the

Upper quadrant sign in the left eye (Mrs. H. H.). Note the net of superficial and deep conjunctival, as well as episcleral, vessels in the upper quadrant of the bulbar conjunctiva, mostly between the 11 and the 1 o'clock meridian.

bulbar conjunctiva of the left eye was moderately congested. The right eye was normal. She had frontal sinusitis and ethmoiditis. The congestion of the upper quadrant cleared up after successful rhinological treatment.

Mrs. H. H., aged 28, had been blinking for a week because the eyes had felt scratchy. Congestion of the upper half of the bulbar conjunctiva (Figure) was present, being most intense in the upper quadrant. The condition was less pronounced in the left eye. She had an incomplete abortion; when this was completed, the eyes cleared up.

Mrs. E. H., aged 45, had noted discomfort from bright light and reading for two months. In October, 1950, she had an episode of labyrinthitis. There was moderate congestion of the bulbar conjunctiva from the upper fornix to the limbus between 11 and 1 o'clock, the congestion being more marked in the right eye. There were a high degree of astigmatism and hyperopia;

1. deRoetth, A. F.: Congestion in Upper Quadrant of Bulbar Conjunctiva, Sign of Focal Infection?, Quart. Bull. Northwestern Univ. M. School, Chicago **18**:193-198, 1944.

corrected vision was 20/30 in each eye. She had esophoria for distance of 1Δ. The near point of accommodation was 16 cm. She had several dead teeth.

Mrs. C. H., aged 66, had experienced a gritty sensation in the left eye for several weeks. She had undergone cataract extraction in both eyes a few years before. Vision with correction was 20/25 in each eye. There were moderate congestion of the upper portion of the bulbar conjunctiva of the left eye and slight congestion of the corresponding area of the right eye. Examinations for focal infection were not done. The patient was living out of town and left for home the same day. Administration of sulfadiazine, 2.5 gm. a day for a week, was ordered. She reported that the eyes felt normal after the therapy.

The differential diagnosis is not difficult, although a number of corneal diseases are associated with quadrantic and sector-like congestion of the bulbar conjunctiva. Corneal diseases, such as phlyctenular, acne rosacea, allergic, and early interstitial keratitis, peripheral infiltration and foreign body of the cornea, and keratoconjunctivitis sicca, can be ruled out by simple inspection, slit-lamp examination, and/or instillation of a drop of fluorescein sodium. Quadrantic and sector-like congestion caused by disease of the limbus and conjunctiva need more careful examination. If there is a lesion in the limbus, such as a phlyctenule, tumor, or foreign body, the vessels all converge toward it, and they are seldom found in the upper limbus. In keratoconjunctivitis sicca and in the bulbar type of vernal conjunctivitis the congestion is localized in the palpebral opening, and in the latter the limbus shows gelatinous, hypertrophic tissue. A concentric collateral vein (Vail and Ascher)[2] occurs in conditions with long-standing engorgement of the conjunctival vessels. It starts near the 12 or the 6 o'clock position, formed by engorged parts of the limbal network, skirts the limbus, and reaches the horizontal meridian. In episcleritis and scleritis the congestion is circumscribed, not like a curtain; and there is a round elevation or nodule at the site of the most intense congestion. The sign of upper-quadrant congestion has most resemblance to the congestion of the bulbar conjunctiva in early trachoma, when there is as yet no corneal change, as seen by gross inspection. However, the other conjunctival signs of trachoma, and the few capillary loops in the peripheral cornea, as seen with the slit lamp, denoting incipient pannus, make it easy to differentiate the two diseases.

In the absence of a local cause, and owing to the hidden location of the sign, which is not in the palpebral opening, a remote cause must be acting. Assuming an allergic pathogenesis of this condition, the following theory is offered. Circulation in the limbal arcades is sluggish. Vogt[3] stated that in normal eyes a large number of these capillary loops do not carry blood, and in some the blood column is interrupted; again, in others the blood may flow alternately in one and in the other direction. It is reasonable to assume that, owing to gravity, the circulation is most sluggish in the arcades of the upper limbus. Blinking and pressure of the upper lid may cause slight passive hyperemia of the upper portion of the bulbar conjunctiva. Under normal conditions this disappears in a few seconds, but if an allergen is circulating in the blood, and is held up here long enough, it may sensitize the vascular wall, or even leave the vessels. Owing to the papillary hypertrophy at the upper tarsal edge in conjunctivitis, the massage effect of the upper lid is

2. Vail, D., and Ascher, K. W.: Corneal-Vascularization Problems, Am. J. Ophth. **26**: 1025-1044, 1943.

3. Vogt, A.: Lehrbuch und Atlas der Spaltlampenmikroskopie des lebenden Auges, Ed. 2, Berlin, Springer-Verlag, 1930, p. 630.

pronounced. Such repeated slight "trauma" in the presence of the circulating allergen leads to sensitization of that portion of the conjunctiva, and later the same allergen produces the allergic inflammation. The allergen may be bacterial, produced by a remote focus of infection, or nonbacterial, e. g., a tissue product.

Among the 20 persons observed with this condition, some were seen only once and could not be subjected to other than ophthalmological examination. All the other 14 persons had a focus of infection, such as infected tonsils, sinuses, or teeth, pyorrhea, repeated colds with tubal occlusion, pharyngeal infection, cystitis, rheumatic fever with cardiac involvement, incomplete abortion, and chronic arthritis. One person had severe chronic constipation. In the past 15 yr. we have become skeptical of the etiologic role of infected foci. Too many times relapse of a uveitis has occurred after eradication of the primary focus. The doubtful role of a focus of infection was impressively demonstrated by Guyton and Woods [4] in a series of 523 patients with endogenous uveitis. They found dental infection in 27.1% and sinus infection in 12.8%, whereas the corresponding percentages in 507 controls with no inflammatory diseases of the eye were 25.8 and 13, respectively. After removal of the foci of infection, the same percentage of recurrences occurred whether the foci were totally removed, partially removed, or not removed. This proves that one has to be extremely critical in accepting an infected focus as a source of an inflammatory disease. Woods [5] has shown that nongranulomatous uveitis is an allergic reaction to streptococci in the great majority of cases, not a bacterial metastasis.

There is evidence that hypersensitivity may develop also to endogenous products, broken-down tissue, and products of metabolism and bring about inflammatory ocular disease; the theory of pigment allergy in sympathetic ophthalmia and the theory of "endocrine allergy" should be mentioned. Zondek, Landau, and Bromberg [6] stated that six patients with keratitis rosacea and acne rosacea faciei of long duration gave positive skin reactions with testosterone, and desensitization treatment with this hormone produced satisfying results. There is a possibility that in the cases of the upper-quadrant sign with chronic arthritis, chronic constipation, and incomplete abortion, other than bacterial allergens were in the circulation.

Therapy for this ocular sign consisted in eliminating the focus producing the supposed allergen. Fourteen persons had a focus of infection. In nine patients who had the focus eliminated the upper-quadrant sign disappeared within two weeks. In one of these the sign cleared up after tonsillectomy but reappeared with recurrence of the exophthalmic goiter, and in another it recurred with a flare-up of arthritis. In two patients the focus (pyorrhea, sinusitis) was not eliminated, and in another the chronic constipation was not corrected. The sign was present in all three persons several months or years later. Two persons could not be reached for a reexamination.

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4. Guyton, J. S., and Woods, A. C.: Etiology of Uveitis: Clinical Study of 562 Cases, Arch. Ophth. **26**: 983-1013 (Dec.) 1941.

5. Woods, A. C.: A Clinical Study of Streptococcus Bacterial Hypersensitivity in Non-Granulomatous Uveitis, English Abstracts of Scientific Papers, Sixteenth International Congress of Ophthalmology, London, 1950, p. 39.

6. Zondek, B.; Landau, J., and Bromberg, Y. M.: Allergy to Endogenous Hormones as a Cause of Keratitis Rosacea, Brit. J. Ophth. **31**: 145-155, 1947.

SUMMARY

An ocular sign, a congested vascular net in the upper quadrant of the bulbar conjunctiva, with no other ocular pathologic condition, was observed in 20 persons. The sign does not fit in any of the recognized textbook diseases. In 14 patients, who could be subjected to examinations, a focus of infection which could have produced an allergen was present. When the focus was eradicated, the upper-quadrant sign disappeared. A theory is offered as to its pathogenesis, according to which the sign would be placed etiologically in the group with allergic conjunctivitis or conjunctival hyperemia.

DESCRIPTION OF AN OPHTHALMOSCOPE FOR EXAMINING THE RETINA IN THE LIVING EYE

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THIS publication contains the description of an optical instrument with which it is possible accurately to observe and examine the retina, as well as the images of luminous objects which may be projected upon it in the living eye. To be of value, such an instrument must overcome two important problems. First of all, as we observe the normal eye its anterior appears to be completely dark. The reason for this, as I shall demonstrate, is that under ordinary circumstances the refractive media of the eye prevent us from observing illuminated portions of the retina through the pupil. Therefore, it was necessary to devise a method to illuminate adequately that part of the retina seen through the pupil. Second, only by looking through the refractive media can we visualize the background of the eye. The phenomenon of refraction projects images of retinal structures in such a way that they cannot be visualized. It is necessary to have a special procedure for producing the illumination, as well as an optical instrument which will allow the observer's eye to focus sharply on the retinal structures.

ILLUMINATION

In order to verify the essential conditions necessary for illumination, we must attempt to explain the reasons for the black reflex seen in the interior of the eye through the pupil.

This black reflex is not a property of the choroidal pigment. Even though the pigment layer could completely absorb the incident light, as do some other black substances, there are tissues present which could reflect a considerable portion of the incident light and thus become visible. This is especially true of the retina, for in the fresh state it is very transparent and is not well demarcated from the pigment layer beneath. It is even truer of the blood vessels of this tissue, since their branches carry sufficient blood to give them a definite reddish hue. Also, in the fundus of the eye there is a shining white area, the position of entry of the optic nerve, upon which there is no pigment; therefore, it reflects all light which falls upon it. However, under the usual circumstances, when we look through the pupil of the living eye, not the slightest trace either of the reddish color of the blood or of the white reflex of the optic nerve can be seen.

That it is the refraction of light in the ocular media and not the color of the background which causes the black reflex of the pupil is readily demonstrated by

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Von Helmholtz was Professor of Physiology in the University of Königsberg.

von Helmholtz, H.: Beschreibung eines Augen-Spiegels zur Untersuchung der Netzhaut im lebenden Auge, Berlin, A. Förstner, 1851.

means of a simple experiment. For this purpose one can use a small camera obscura with a thoroughly blackened interior, really an artificial eye, and at the site where the image is projected one can place an opaque white panel, such as a piece of thick white drawing paper. If desired, the ocular tube of most microscopes could be employed after the ocular lens has been removed, but with the objective lens remaining in position. Such a tube usually has exactly the same length as the focal distance of its objective lens. Then, if the end of the tube from which the ocular lens has been removed is set upon a white panel, the construction of the required camera obscura is completed. Even though very bright images of the surrounding illuminated environment may, under these conditions, be projected onto the white panel, if an attempt is made to peer through the lens from any angle whatsoever the interior of the instrument appears to be completely dark. Thus, we have here an ingenious model of the eye, in which the objective lens of the camera corresponds to the cornea and crystalline lens, and the white sheet of paper to the retina; but here, as in the eye itself, the inner chamber remains completely dark so long as the sheet of paper is placed exactly at the position where the images of the outer environment are brought to a focus. If the convex lens is then removed, or if the distance between it and the sheet of paper is changed materially, the observer can readily visualize the white surface of the paper.

How can refraction of light produce this phenomenon? To explain it, we must make use of the physical laws of refraction to trace the path taken by the light rays in the eye.

When light from a luminous point is allowed to fall on a suitably accommodated eye, we infer that the light is focused exactly; that is, all rays of light which arise from the luminous point are concentrated once again at a single point on the retina. The major portion of this light, caused by the ocular media to converge on the retina, is absorbed by the black pigment; but a small part of it is reflected from the neural elements and blood vessels and a part from the layer of rod-shaped cells. As was shown by E. Brücke, the light which returns from the latter structures passes again through the pupil, without being dispersed to other portions of the interior of the eye. In this way, the dissemination of perceptible quantities of scattered light rays within the eye is avoided. The returning rays, which pursue a divergent course through the refracting surfaces of the eye from the convergence point on the retina, traverse exactly the same path, but in the opposite direction, as that which the rays of light from the luminous point used in converging upon the retina through the refracting surfaces of the eye. It is therefore obvious that the reflected rays of light, after traversing the refractive media and leaving the eye, must coincide exactly with the incident rays, and all must again return to the original luminous point.

Thus, if two rays, coursing in opposite directions through a simpler refractive medium, coincide in one portion of their course, they must do so throughout. The angle of incidence of the departing ray is identical with the angle of refraction of the entering ray at the limiting surfaces of the medium within which they coincide. According to the laws of refraction, the ratio of the sines of the angle of incidence and of the angle of refraction of the departing rays is just as large as the similar ratio of the sines of the angle of refraction and of the angle of incidence of the entering rays. Therefore, on the other side of the refracting surface, the angle of refraction of the departing rays and the angle of incidence of the entering rays must be equal. Since all these rays coincide in the first plane [the plane of refraction],

we must conclude that they also coincide in a second medium. Similarly, this holds good for a third, or fourth, or more media.

If we now construct a suitable system of refractive surfaces so that a luminous point, *a*, is brought to a sharp focus at point *b*, meaning that all rays which emanate from *a* are again focused at *b*, we can prove the well-known fact that if rays were to be emitted at *b* they would be focused at *a*. In other words, any rays which pass from *a* to *b* will return from *b* to *a* along exactly the same course. If, then, we designate *a* as a luminous point outside the eye and *b* as its image at a point on the retina, we find that the ocular media focus the emergent rays from *b* once again into an image at *a*. The image of the illuminated point on the retina thus coincides with the original luminous point. This concept still applies when we deal, not with a luminous point, but with a luminous surface or object, provided the eye is exactly accommodated for the outline of this surface or object. Hence, all the incident light which is reflected must return to its origin and can never take another direction.

Therefore, it is impossible to visualize the illuminated portions of the retina without special equipment. Furthermore, we cannot bring our eyes into the pathway of the returning light without completely interrupting the incident rays. No light can enter our pupils from the interior of the eye of another person unless the light emanates originally from our own pupils. And since, as a rule, no such light comes from our own pupils, we see in the darkness of the other pupil only a reflection of the blackness of our own pupils; only those portions of the other retina on which our own dark image is reflected are evident.

Up to this point we have assumed that absolutely sharp images are formed in the eye that is being observed. When this is not the case, the foregoing propositions are not universally applicable, and the reflected light may largely return to the luminous object. However, a portion of the reflected light may pass by, so that an observer who is situated very near to the line of direction of the incident light may be able to perceive a portion of the reflected light. This fact forms the basis for the methods of Cumming [1] and Brücke [2] for observing the illumination of human eyes. From what has been said, it is evident that the less exactly the rays emanating from a luminous point are focused on a point on the retina, the more intense the illumination will be, especially when the eye is not exactly accommodated. Furthermore, I am fairly well convinced that one can, with Brücke's method, detect a slight luminosity even in eyes with good visual acuity and with accurate accommodation for the luminous object; therefore, we must postulate that under most circumstances there is slight scattering of the incident light to the sides. This is probably due to slight inaccuracies in the eyes, incomplete transparency of the refractive media, or diffraction at the pupillary margin.

However, in these investigations it is possible for the observer to perceive only a small fraction of the returning light. In fact, he sees only those irregularly refracted rays which are of no use in the production of a definite image. For our purposes another method must be employed to make it possible to peer into the eye in exactly the same course as that of the incident light, and not merely approximately in this direction. The means whereby this could be done was discovered accidentally by von Erlach and investigated by Brücke. Von Erlach, who wore

1. Cumming, W.: Med.-Chir. Tr., London **29**:283, 1845-1846.
2. Brücke, E.: Arch. f. Anat., 1847, p. 225.

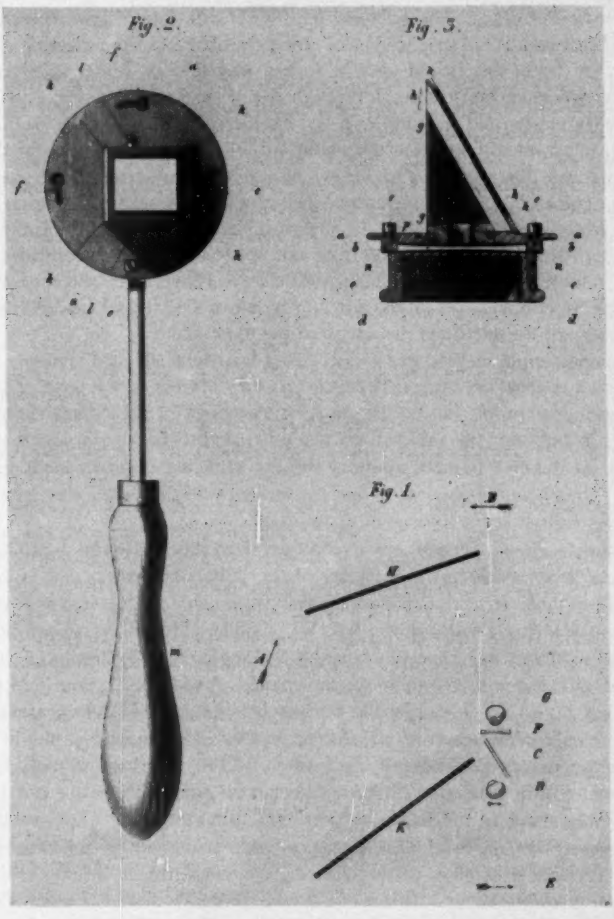
spectacles, noted that the eyes of a friend would be illuminated if the latter looked directly at the image of a light reflected in the lenses of the spectacles. Unmounted lenses also could be used as illuminating mirrors, and the observer likewise could see through these into a subject's eyes. We employ exactly the same procedure, but advantageously replace the spectacle lenses with carefully ground plane lenses.

In a darkened chamber containing only a single light source, either a lamp with a bright flame or sunlight admitted to the room through a hole in the window shutter, we can set a small plane glass plate in such a position that the subject can see the reflected image of the light, although he need not look directly at this reflection. Light is thus directed into the subject's eye from the anterior surface of a lens, and the observer can simultaneously examine the eye through this same lens without being aware of the light reflected from the anterior surface. It is evident that in this way it is possible to direct the line of vision into the subject's eye in exactly the same direction as that of the course of the light. Under such conditions, the observer's eye will receive light from the depths of the other eye, and the pupil will be illuminated.

In Figure 1, let *A* be the flame, *C* the glass plate, *D* the observed eye, and *G* the observing eye. The light from point *A* which impinges on the surface of the mirror is partially reflected, and the reflected portion, according to the laws of catoptrics, has a course as though it had been projected from an image of the flame at *B*. For the subject's eye this reflected image replaces the luminous object, and on his retina a smaller, inverted image is projected. Moreover, the axis of this eye can, if desired, be turned somewhat toward the object, *H*. In accordance with previous statements, the refractive media of *D* will project the image of its retina and of the retinal images to *B*. *B* is therefore the apparent object for eye *D*, and the rays which return from the latter must go back again to their place of origin. On the way from *D* to *B* this light again encounters the mirrored plate, and a portion is reflected and returns to the real flame, *A*, while the remainder passes through the glass and enters the eye of the observer, *G*.

This procedure causes the pupil of the eye *D* to be illuminated with a reddish glow, much more brightly than when the method of Brücke is used. When his technique is employed, the illumination of the eye is accomplished by merely the very small amount of light which is not completely refracted. On the contrary, with my method, the entire light is used, with the exception of the portion (admittedly not inconsiderable) which is lost by passage through the reflecting glass. Moreover, the strength of illumination varies according to which portion of the retina receives the image of the flame. The bright retinal image must always lie on the prolongation of the line *BD*; and therefore if the eye *D* is turned in different directions, the image must be focused at various positions on the retina. If it falls on the optic disk, most of the light is reflected, and the pupil is illuminated with a bright yellowish white light, almost as though the flame were situated immediately behind the pupil. The retina proper, however, reflects much less light, principally red light. In general, the image of the flame is stronger the nearer it is to the optic disk, and weaker the farther away it is from this disk. On the contrary, the yellow macula, the site of direct vision, which is used when the observed eye, *D*, gazes directly at the reflected image of the flame, at *B*, returns much less light than do the neighboring structures, and therefore is not of value in this investigation.

In order to fulfill the condition that the observer gaze into the eye exactly in the direction of the incident light, the glass plate can be adjusted by either the subject or the observer. If the former does so, he must set the glass plate so that he can see in it the image of the flame. Moreover, this image must appear to the subject to come from exactly the same direction as the observer's eye, and the latter and



Copperplate reproduction accompanying the original article.

the reflected image must appear to coincide. In this way the established conditions may be fulfilled. However, this method has the fault that the subject must look directly at the flame, and the retinal image therefore will be focused just at that point from which the least light is reflected. Moreover, if the subject, after he has found the correct direction, moves his eyes slightly sideways in order to intensify

the illumination, then the pupil will be displaced and the proper setting will be disturbed. Some assistance may be obtained if the mirror is turned slightly to and fro.

It is much better, however, to carry out the experiment in the other manner, whereby the observer himself holds the lens. This method requires that the subject's face be shaded and the reflecting plate be made so small that it is just large enough to see through. The reflected light then will appear upon the shaded face of the subject as a small bright spot of about the shape of the reflecting glass. The observer must aim this bright spot in such a way that its center falls on the subject's eye, while he himself peers through the lens. In this way the lens may be aligned very easily, and the subject's eye can be turned to all sides without much difficulty, to permit the image of the flame to fall upon various parts of the retina.

Anyone can illuminate one's own eye in a similar fashion with the assistance of a piece of plane glass. One must stand before a mirror, set up a lamp at one side, hold the lens before the right eye in such fashion that one sees the flame reflected therein, and turn it just enough so that the image of the flame coincides with the reflected image of the left eye. Then the left eye observes in the mirror that the right pupil is luminous, even though faintly, since the retinal image falls toward the periphery of the eye quite distant from the optic disk.

The same simple method can be utilized advantageously to illuminate any dark cavity with a narrow opening, such as the auditory meatus or the nose. To visualize the tympanic membrane, the subject must be placed with his back against a window, preferably in sunlight; the auricle must be drawn slightly backward, and the reflected light must be directed into the auditory meatus while the observer looks in through the lens. Thus it is possible easily and conveniently to illuminate the drum head to any degree desired for purposes of examination.

Any simple glass plate will serve as a mirror to illuminate the pupil. One need pay very little attention to the intensity of the light. However, if it is desired to examine closely the structure of the retina and the nature of the image of the flame, one must attempt to get as bright a light as possible. This objective can be reached in two ways—either by properly adjusting the angle made by the incident light or by increasing the number of the reflecting plates. I wish to explain here the principles which guided me in developing the construction of my instrument, and which could serve ophthalmologists as a basis for further modifications of the instrument for clinical purposes. For those of my readers who may find the physical equations to be presented too unfamiliar, I must say that in general these are not necessary for fully understanding the following sections.

The greater the angle of incidence, the more light will be reflected from the bounding surfaces of a glass plate. The angle of incidence is the angle subtended by the path of the light rays with a line drawn perpendicular to the surface. Since light waves oscillating in various directions behave differently after being reflected from the upper surface of a transparent body, we must divide the incident light into two equal portions, of which the one is parallel to the surface of the mirror and the other is polarized perpendicular to it. The intensity of the entire incident light is designated by J, and the portion previously mentioned is $\frac{1}{2}J$. The angle of incidence (angle between the incident rays and the perpendicular) is designated as α; the angle of refraction (between the refracted rays and the perpendicular), as α_1, and

the index of refraction, as v. Given α, we can determine α_1 by using the equation

$$\sin \alpha = v \sin \alpha_1$$

The intensity, P, of the light reflected from the bounding surface between air and glass, and polarized vertically to the plane of incidence, is, according to the formula of Fresnel $P = \frac{J}{2} \cdot \frac{\tan^2 (\alpha - \alpha_1)}{\tan^2 (\alpha + \alpha_1)}$.

Likewise, the intensity, Q, of the reflected light polarized parallel to the plane of incidence is $Q = \frac{J}{2} \cdot \frac{\sin^2 (\alpha - \alpha_1)}{\sin^2 (\alpha + \alpha_1)}$.

If several reflecting surfaces are arranged parallel and one behind the other, and the illuminated surface is large enough that the reflected images which are produced by the various mirror surfaces superimpose themselves upon the observed eye, the various images are combined into one of greater brightness. By calculating the amount of light reflected back and forth between the various surfaces, it is possible to determine the total amount of light reflected in any system of parallel surfaces. For an unknown number, n, of reflecting surfaces, the sum, II, of light polarized perpendicular to the plane of incidence is as follows: $II = \frac{n P}{J + 2 (n-1) P} J$, and the sum, Σ, of that polarized parallel to the plane of incidence is $\Sigma = \frac{n Q}{J + 2 (n-1) Q} J$.

Since I have been unable to find these formulas in any of the literature pertaining to physics, I have added a brief derivation of these formulas in the appendix to this monograph.

The values $II + \Sigma$ represent the total amount of light reflected from the mirror surfaces and falling upon the observed eye. This total value can be designated as H, so that $H = II + \Sigma$.

When the size of the pupil remains constant, the degree of brightness of the retinal image is proportionate to the quantity of light. The quantity of light returning from the eye may be designated as mH, where m is a coefficient the value of which remains the same no matter what the intensity of the light, but which is dependent upon the nature of the site on the retina from which the light comes. The returning light reenters the mirror system and divides into a part which is again reflected and a part which penetrates the system. Only the latter portion enters the eye of the observer. Light reflected by the retina no longer is polarized (this being generally true with diffuse reflected light), in this respect having an action similar to that of the rays from the light source as they strike the mirror. Since this light impinges upon the surfaces from the same angle, proportionately as much of it is reflected and transmitted as was the case when the light first came from the source. If we designate the transmitted light by X, we have the ratio $X : mH = (J - H) : J$. From this ratio can be computed the quantity of light, X, which enters the eye of the observer. H may equal O, or it may equal J; that is, if no light or all the light is reflected, then $X = O$. Between these bounding values of H there is a maximal value for X which can be computed according to the established rules of differential calculus. The maximum occurs when $H = \frac{1}{2}J$. Then $X = \frac{1}{4} mJ$. By using these equations, it is possible to compute the angle of reflection which gives the brightest image to the observer for a known number of mirror surfaces. Unfortunately, the equation which expresses the dependence of the value H upon the angle of incidence, α, cannot be solved for α; we can, therefore, by experimental calculations find the proper values for α only roughly. However, it is hardly worth while to strive for

highly accurate figures for this entity, because, first of all, the degree of brightness perceived by the observer is not materially different even when the position of the lenses does not give the maximum, and, second, the alterations in size of the pupil with different intensities of the incident light cannot be calculated accurately.

Since stronger illumination will cause the pupil of the observed eye to contract, an increase in the value of H will not cause a proportionate increase in the brightness of the retinal image, as it should according to the formulas already developed. It is therefore more advantageous to use a somewhat smaller value for H in the instrument than was necessary to obtain a maximum for X in the foregoing calculations. A value deviating slightly from the foregoing maximum is obtained; that is, $X = 1/5\ mJ$ if the light is reflected from one glass plate at an angle of about 70 degrees, from three plates at an angle of about 60 degrees, and from four plates at an angle of 55 degrees. These positions, therefore, are approximately the most efficient.

Consequently, it is possible to obtain sufficient brightness even with a single glass plate as a mirror. However, the use of several plates with a smaller angle of incidence has distinct advantages if clear retinal images are desired. First of all, glass plates, even though their surfaces are ground parallel, do not always have so homogeneous an internal structure as to transmit good, clear images obliquely. Second, when the incident light is strongly oblique, it is much more difficult to direct the reflecting plate correctly toward the subject's eye, and much more difficult to hold it there. Moreover, the lateral portion of the observer's head much more readily interrupts the light rays which should fall on the mirror. This is especially difficult to avoid when the angle of incidence exceeds 70 degrees. Finally, it is important to consider that a small portion of the light which strikes the eye of the subject is reflected from the cornea and appears to the observer as a pale light spot in the field of vision. This spot is situated in the center of the pupil if the subject directs his eye straight at the mirror and if he looks directly at the reflected image of the flame. The reflex is situated more laterally if the eye is turned in another direction, but this more or less hinders good visualization of the retina. It is of distinct advantage to the observer if the intensity of the corneal reflex can be considerably diminished. This reflex appears to be much less prominent when four plates at an angle of 56 degrees are used than when either three plates at a 60-degree angle or one plate at a 70-degree angle is employed, although the retinal image previously described retains practically the same intensity of illumination. Even with variation in the number and position of the plates, the apparent brightness of the corneal reflex is not proportional to the brightness of the retinal image because the light which enters the eye of the subject is partly or entirely polarized by reflection and becomes depolarized by diffuse reflection from the retina. This is a phenomenon which does not occur in the case of the specular corneal reflection. If the cornea reflects the portion μA of the total quantity of incident light, A, then in our investigations the quantity of light which reaches the observer's eye from the cornea (using the same principles and designation as before) equals $\frac{\mu\ II\ (J - 2\ II) + \mu\ \Sigma\ (J - 2\ \Sigma)}{J}$. Calculation gives the solution previously noted. Therefore, from every point of view, the necessary intensity of light is more readily obtained by increasing the number of plates (since they reflect the light below the polarization angle of 56

degrees) than by increasing the angle of incidence because the corneal reflex can be entirely avoided by greatly multiplying the number of plates.

Throughout the previous discussions I have assumed that the flame of a good oil lamp with a double air draft would serve as the source of light. In a most carefully conducted investigation, the light was not reflected so strongly that it would seriously dazzle or fatigue the peripheral portions of the retina of the subject. Therefore it is possible very easily to carry on the observations as long as desired. It is only when the eye looks directly at the reflected image of the flame that this degree of brightness cannot be long endured. If a more intense light is available, such as sunlight, which can be made to enter a dark room through an opening in the window shade, it is possible to see the retinal image much more distinctly. The light, after being sufficiently dimmed, is permitted to be reflected as perpendicularly as possible from the mirrored plates, rather than obliquely. The quantity of light allowed to enter the eye is limited mainly by the sensitivity of this structure. If, after reflection, very strong light which exceeds these limits is available, and if it is not simultaneously dimmed in some other fashion, the observer is able to visualize most brightly the retinal image which was reached at the limits of endurable intensity, provided that the least possible is lost at the second reflection. This is certainly the case when the light from a single plate is reflected almost perpendicularly.

I have not had the opportunity to conduct such an investigation with sunlight. However, I do not believe that any significant advantage is to be gained in this way, since with perpendicular reflection the apparent brightness of the annoying corneal reflex increases to a much greater extent than does the brightness of the retinal image.

What appears at first glance to be a plausible supposition has several times been suggested to me, that is, that the quantity of light entering the eye, and also the brightness of the retinal image, could be considerably increased by the use of a convex lens. This would concentrate within the observed eye all the light directed toward it. At this time, however, I wish to call attention to the fact that this procedure will increase only the size of the retinal image, not the brightness. If the eye is placed where the light rays are brought to a focus by a lens, the entire surface of the lens will be illuminated with an intensity approximating that of the luminous point. Instead of the smaller retinal image of the luminous point being formed, a larger image is produced with the same intensity: that of the surface of the lens. Moreover, there is no complicated combination of lenses which will increase the brightness. In order to understand this, we need only remember, from the theory of the telescope, that no telescope or other similar combination of lenses can make an object of known diameter appear any brighter than it is when seen with the naked eye. Just as the possessor of the observing eye subjectively perceives the surface to be no brighter through the lenses, the retinal image within his eye objectively can be seen to be no brighter with or without these lenses. Therefore, an objectively brighter retinal image must always correspond to a stronger subjective perception of light.

FORMATION OF A CLEAR IMAGE OF THE RETINA

We are now about to investigate the method by which, using light returning from the subject's retina and entering the eye of the observer, we can obtain clear images of the retina itself and of the images of the source of light superimposed

upon the retina. Again, we can make use of Figure 1 for this purpose. According to the previous description, the rays returning from a point on the retina of eye D are so refracted by the ocular media that they again converge outside the eye as the corresponding image, B. The image of the retina and the retinal image of the flame which are projected through the ocular media coincide in size and position with the first mirror image of the flame. An observer who, calculating from the mirror, is stationed on the far side of B, and at a distance from the most distinct view of B, would now actually be able to see clearly the above-mentioned image of the retinal structures. His field of vision, however, limited as it would be by the pupil of the observed eye, would be so small, as a consequence of the comparatively great separation of the two eyes, that it would be impossible to combine the observed details into one complete image.

This problem of widening the field of vision makes it imperative that the observed and the observing eye be brought as close together as possible. However, in that case, the image, B, generally would be situated behind the observer, and he would not see it clearly. If the eye of the observer be placed, for example, at G in Figure 1, it will receive the light rays which emanate from the eye D and converge toward the point B. A normal eye can focus on its retina parallel rays which come from infinity, as well as divergent rays which arise from a nearer point, but not converging rays. The simplest method of altering these rays and causing a converging bundle of rays to diverge is to insert a concave lens between the mirror and the eye of the observer, such as F in Figure 1.

According to the known laws of refraction by concave lenses, the converging rays entering F will, after their exit from the lens, be less convergent (if the focal distance is greater than FB), or parallel (if the focal distance equals FB), or, finally, divergent, as though they emanated from the points of an image, E, behind the subject eye (if the focal distance is less than BF). In the last situation the concave lens has exactly the same function as in opera glasses, in which the apparently inverted image which the objective lens should project at its focal point, and which is situated on the side of the observer, is converted to an upright real image. This image appears to the observer to be situated on the far side of the lenses. In our problem, the ocular media act as the objective lens of a microscope which is constructed according to the principles of the Galilean telescope, while the concave lens represents the ocular.

If the values for the accommodation of the two eyes are designated as BD and EG, and if the distance separating the two eyes and the concave lens is set according to the principles given above (that is, as small as is permitted by the mirror), then it will be possible to calculate the focal distance of the concave lens according to the known laws of refraction of lenses. This equals

$$\frac{EF \cdot BF}{EB} \text{ or } \frac{(EG - GF)\ (BD - DF)}{EG + BD - DG}.$$

The greater the values of accommodation EG and BD, the greater also must be the focal distance of F. Thus, when one of the two eyes is myopic, stronger concave lenses must be used; but when one eye is hyperopic, it is necessary to employ weaker concave lenses than would be needed for two normal eyes. If the observing and the observed eye exchange roles without altering the status of accommodation, a lens of different focal distance usually is necessary; and indeed, since GF exceeds DF, a weaker lens is needed if a myopic eye becomes the observer instead of the subject.

However, a closer consideration of the foregoing formula reveals that this difference is extremely small in eyes which are not too highly myopic. Consequently, in these subjects the selfsame lens will suffice for reciprocal observations.

The magnification can be calculated by the known laws of optics as follows: The image, *E*, must appear to have the same visual angle as does its apparent object, *B*, measured from the center of the lens, *F*. Since the eye *G*, the lens, *F*, and the eye *D* are as near each other as possible, then *B* will appear only slightly larger when viewed from *F* than it would when viewed from *D*. Therefore, the eye *G* sees the retinal image of the flame in about the same size as, or perhaps a trifle larger than, the eye *D* sees the original flame, if measured exactly. The portion of the retina upon which the image of the flame falls similarly appears as the image, *E*, magnified in the same proportion as the image described above.

According to what has just been said, the ratio of this magnification is that of the retinal image to its object. If we assume that the distance of the point of intersection of the unrefracted rays from the retina is ⅓ inch (8.5 mm.), according to Volkmann's measurements, and the distance of the objects from the eyes is the normal visual distance of 8 in. (20.3 cm.), then the magnification is found to be twenty-four-fold.

In our investigations we have compared the ocular media with the objective of a microscope and the concave lens with the ocular. Now, at the site of the latter we should be able to place a combination of two convex lenses which are separated from each other by less than the sum of their focal lengths, just as is done in the ordinary compound microscope. The first of these lenses would, as in the collective lens of this instrument, more rapidly focus the slightly converging light rays coming from the eye of the subject. This would produce an image lying between this lens and its focal point, producing an upright image of the flame and an inverted retinal image. This image would then be magnified when seen through the second convex lens. I have studied the effects of such a system, according to the known laws of optical instruments, in relation to magnification, brightness, visual field, etc. Since these calculations reveal that no essential advantage would be gained from the use of such a system as compared with the simple concave lenses, only a brief résumé of the results is necessary here. We must assume that the first lens, in so far as permitted by the mirror, is placed very near the eye of the subject and that the eye of the observer is approximated to the second lens.

With reference to illumination, the maximal brightness is obtained through a concave lens in the middle of the visual field. If we wish to obtain the same results with two convex lenses, these must be selected and arranged so that no further magnification is permitted than occurs when the concave lens is used; that is, the observer's eye must see the magnified retinal image of the flame at the same visual angle as that with which the subject's eye sees the reflected image of the flame.

If any magnification is to occur, the image of the first lens must be formed in the middle between the two lenses, as it does in the ordinary ocular tube of the compound microscope. It is possible, with less magnification, to permit the greater part of the visual field to be maximally illuminated; on the contrary, if greater magnification is used, this may not even take place in the center. Even though a higher magnification would be very advantageous, it is not possible to make use of it, since the illumination decreases so greatly. Furthermore, the living eye does not tolerate well for any length

of time a quantity of light stronger than that reflected from a good lamp without being dazzled. Moreover, the living eye cannot be held sufficiently quiet for good fixation of various parts of the image, as would be necessary if higher magnification were used.

The visual field is next to be considered. That part of the retina which can be seen becomes smaller the farther the observer is from the subject's eye, and becomes greater when the observer is nearer. Proximity is limited by the fact that the obliquely set reflecting plate must be inserted between the eye and the glass lenses.

In order mathematically to compare the action of the various lenses, we must assume that the separation of the concave lens and that of the first convex lens must be equally great. If, then, we make use of the fact that the illumination attains its maximum in the center of the visual field, it is possible to find certain focal lengths which make the visual field the largest for every given distance from the eye. If we employ the focal lengths of the two convex lenses in this way, we find that if the distance of the lens from the eye is smaller than the focal length, the two convex lenses can produce a larger visual field than a concave lens (this is shown by the fact that the objective of a telescope can be held away from the pupillary aperture without affecting the clarity of the image, and this may be noted with achromatic lenses with focal lengths less than about 10 times the pupillary diameter). Now it is true that even when the lenses are as close as possible to the observer's eye, the distance between the two with regard to the insertion of the mirror usually is somewhat greater than 10 times the pupillary diameter; therefore, with the use of two convex lenses there would be a very slight increase in the visual field. To attain this, however, focal lengths of 3 to 3⅓ in. (7.6 to 8.5 cm.) must be employed, and with these it is very difficult to get an image of the same clarity as is obtained with a concave lens, which can have a focal length of 8 to 10 in. (20 to 25 cm.). In my opinion, there is no advantage in employing the convex lenses. Experiments with such lenses have shown that the correct placement of the instrument for the observation of the retinal image is much more difficult to obtain. If a simple concave lens is used, exact alignment of the axis of the lens on the observed eye is not necessary, and the mirror need merely direct the light correctly. There must be exact alignment, however, if two convex lenses are employed.

Thus, it appears to be advantageous to employ the simple concave lens as the ocular, although almost everywhere else in optics it is more advantageous to employ convex lenses. These likewise do have an important advantage in this experiment, for sometimes their use is to be desired; by merely changing the distance between the lenses, it is possible to adapt the apparatus to all distances through which the observer's and the subject's eyes are moved. In order to accomplish this with a concave lens, varying strengths of lenses are necessary. If it were possible to fixate the instrument and the head of the subject, then convex lenses would be more convenient; but without such an arrangement all their other advantages are outweighed by the disadvantage of difficult adjustment of the instrument. Therefore, I have always used only a simple concave lens.

DESCRIPTION OF THE OPHTHALMOSCOPE

In order to begin observations, as described above, it is convenient to combine the mirror and the concave lens in a suitable frame. I have chosen the name *Augenspiegel* for this combination because of its analogy to similar instruments of this name. This instrument is seen in frontal view in Figure 2 and in horizontal cross

section in Figure 3. The mirrors, *hh*, are fastened by means of the brass piece, *gg*, against the circular plate, *aa*, with an angle equal to that of the chosen angle of incidence of the light rays (in the figure, 56 degrees). The brass piece, *gg*, forms a hollow triangular prism with the glass plates. A view of the inner chamber is obtained in Figure 3, and the right-angled triangular area is visible. Of the three quadrangular surfaces of the prism, the one corresponding to the hypotenuse of the figure is formed by the glass plates; the one corresponding to the longer side remains free, while the shorter side lies in the disk, *aa*, and has a cylindrical process, *p*, which penetrates a corresponding circular opening in the plate, *aa*, in such fashion that it holds the prism tightly to the disk but permits rotation about its axis. The glass plates are pushed against the prismatic brass piece by the frame, *kkkk*, the overlapping rims of which are fastened to the brass piece, *gg*, by the screws, *ll*. The disk, *aa*, is joined, but not permanently fastened, to the cylinder, *bbcc*. In the rim of *aa* have been cut four openings, *f*, which correspond to four screws, *ee*, with cylindrical heads and thinner necks set into the rim of the cylindrical ring, *bb*. So that the holes, *f*, can be seen clearly, only two of these screws are shown in Figure 2. The heads of the screws may be thrust through the wide circular portion of the opening, *f*, and if then the disk, *aa*, is rotated about its midpoint, the necks of the screws enter the smaller, slit-like portion of the same openings, while the heads overlap and fasten the disk to the ring, *bb*. In this way it is possible easily and quickly to disengage the disk from its fastening to the concave lens and to replace the latter with another. The concave lens, *nn*, is inserted between the plate, *aa*, and the bottom of the cylindrical portion, *dd*, which is screwed into *bbcc*, and can be set back by unscrewing if it becomes necessary to superimpose two lenses for very myopic eyes. The entire apparatus is fastened to the handle, *m*. For observers with normal eyes the ordinary concave spectacle lenses numbered 6 to 12 usually are sufficient for examination of all adaptive positions of the eyes which are to be investigated. For visualizing normal eyes I usually employ No. 10. For examining the eyes of very myopic persons, it is necessary to superimpose two lenses.

With regard to the reflecting plates, an ordinary mirror is not suitable because the two surfaces generally are not sufficiently parallel that they can superimpose exactly the images of the flame of the lamp thrown on them. Therefore, for our purposes, the lenses must be specially ground in order that parallel surfaces may be procured. However, this stipulation need not be carried out with such precision as is necessary in the plane-parallel glasses used in the finer measuring instruments.

Good blackening of the nonreflecting surfaces is essential. Since only a proportionately small amount of the bright light which strikes the instrument is reflected back from the subject's retina, all the remaining light which might possibly enter the eye of the observer must be carefully eradicated. First of all, the inner surface of the ocular piece, *dd*, must be blackened and the observer must press his eye as closely as possible into the ocular in order to exclude all extraneous light which might come from the flame onto these surfaces. Second, the outer surface of the disk, *aa*, and of the prismatic mirror frame, *kkkk*, must be blackened so that bare metal parts which are directed toward the observed eye will not produce disturbing corneal reflexes. Third, the inner side of the mirror frame should be blackened with especial care. The light of the flame which strikes the reflecting plate passes through, in greater part, and strikes the plate, *gg*. All light that is not absorbed here is returned to the mirror again. From here the light is reflected into the observer's

eye in the same direction as that of the weak light from the subject's retina, and it mixes with the image of this membrane. I have found that in this situation the usual procedure used by mechanics to blacken brass objects is inadequate. I have therefore lined the inside of the frame of the mirror with black velvet, which absorbs the light much more thoroughly.

To use the instrument, the observer places the subject in a darkened room near the corner of a table upon which a well-burning double-draft lamp, without an opalescent chimney, is set at the same level as that of the eyes and lateral to the face. It is advantageous to place on the table, at a suitable visual distance, a dimly lighted object upon which the eyes of the subject can fixate at definite points; an example would be a blackboard divided into quadrants, each of which is designated by a number. Then, if the eye is permitted to fixate the various quadrants one after the other, the image of the flame will fall on different portions of the retina, which then may be investigated by the observer in any order desired. An opaque screen must be erected between the flame and the eye of the subject so that the eye may be in shadow, since otherwise a disturbing corneal reflex might appear and the pupils would narrow if the direct light of the flame were to strike the eye. Indeed, the border of the shadow must pass very close to the observed eye in order that the ophthalmoscope, which itself must remain in the light, may be brought forward as close as possible to the eye. The observer is seated in front of the subject. Without first looking through the ophthalmoscope, he directs it in approximately the right direction, whereupon a brightly illuminated spot is cast on the face by the reflecting surface. Then the mirror is turned in such fashion that the middle of this illuminated spot falls on the eye, and if the axis of the instrument is correctly aligned, he looks through. Generally, the bright image of the flame then is seen directly ahead, or it can be located after several to-and-fro movements. Moreover, it is possible when looking through the instrument to visualize the eye and the light which falls upon it; and, even though they are seen very indistinctly, the correct position may be found with their help. If the retina is not seen clearly, but the pupil appears illuminated, a different concave lens must be employed. An observer who has trained himself to alter voluntarily the accommodation of his eyes can easily determine whether he sees more clearly with far-sighted or with near-sighted accommodation and whether he therefore needs more or less strongly curved lenses. Moreover, many persons make the matter difficult, especially those who are unaccustomed to making observations through optical instruments and those who are myopic, since they involuntarily accommodate their eyes for great nearness because they consider the object to be seen as being very close. When this occurs, the eyes of the observer become greatly fatigued; they easily become congested and start to water. As with all optical instruments possessing a focusing device, it is necessary in the use of this one to accommodate the eyes for infinity and then to adjust the instrument to the eye.

After some practice, it is not difficult to find the right lens and the correct positioning of the instrument. Furthermore, one can very easily demonstrate on one's own eye to the student who has never seen this phenomenon what he should look for. In this way it is much easier for the student independently to observe the very same things in other eyes. To this end, the instructor determines, first, the lens through which he can clearly see the retina of the student, and he places this in the ophthalmoscope; then, through this combination the student, in turn, can see clearly into the eye of the teacher if neither of the two is very myopic. In the latter event,

as noted previously, the more myopic person requires a somewhat weaker lens when he is the observer than he does when he is the observed. The instructor then places one of his own eyes in the position described for the eye of the subject, and he must hold the ophthalmoscope in such a position in front of him that he can simultaneously see through its central opening and note the reflected image of the flame in the mirror. Next, he gives the instrument to the student in the same position and allows him to look through it. The student then observes the image of the flame in the eye. To acquaint him with the appearance of various parts of the retina, the instructor lets the image of the flame fall onto the place of entrance of the optic nerve, since it is here that the largest and most recognizable vascular trunks are to be seen. To accomplish this, the eye must gradually be turned medially from the reflected image of the flame until this image appears suddenly to disappear or to grow smaller. This takes place, as is well known, when the image falls upon the place of entrance of the optic nerve. Moreover, most people are more successful in seeing and recognizing the image of the flame than they are in seeing and recognizing the tiny parts of the retina in the bright background.

VISUALIZATION OF THE RETINA AND THE IMAGE OF THE FLAME

If one is desirous of examining the retina thoroughly, it is necessary, as mentioned previously, to erect a numbered blackboard to use as a fixation point for the eye of the subject. As soon as the eye fixes one of the numbers, looking slightly inward past the mirror, the observer is almost always able to discern one or two large vessels in the field of vision. He then permits the eye to turn toward an adjacent number and notes whether he approaches nearer the origin or nearer the termination of the vessels. If he continues in this manner to follow the course of the vessels in the direction of the larger branches, he approaches finally the place of entrance of the optic nerve. This structure is distinguished from the rest of the background of the eye by its whiteness, because it is not covered by pigment or a fine vascular network; instead, the white cross section of the nerve lies quite free, at most penetrated by a few fine vessels. Usually, the arteries and veins of the retina arise from the medial portion. Occasionally, one can see a portion of the vessels still buried in the substance of the nerve and can appreciate that this substance must be very strongly transparent in the living state. It is possible to distinguish the two types of vessels, one from the other, by the brighter color of the blood and the double contour of the walls of the arteries and their first branches. I have not been able to observe pulsations with certainty. The first main branches of the vessels border the optic nerve on the inner side and later branch out, above and below, over the expanse of the retina. The appearance of the sharply demarcated red vessels upon the bright white background is of surprising elegance. Somewhat farther medially, but rather near the nerve, I have always noted a small sickle-shaped, shadowy stripe, which appears to arise from a wrinkle in the retina.

In other parts the background of the eye looks red; indeed, near the optic nerve and around it, it looks pink, but it becomes somewhat darker the farther one goes away from the nerve. Here are seen larger and smaller blood-red branching vessels, which may be clearly distinguished from the background. The background itself appears not to be entirely homogeneous, but indistinctly reddish. This seems to arise from the fact that the narrow capillary network is too delicate, is illuminated

too faintly, and is too transparent to be clearly distinguished from the underlying light-gray tissues of the retina. That the background in the vicinity of the optic nerve appears to be brighter may well be due to the fact that here the retina is thicker, as a consequence of the superimposed layers of nerve fibers; it is always thinner toward the periphery. The site of direct vision (the yellow spot) is especially well distinguished from its immediate surroundings. In order to bring this spot into view, the subject's eye must gaze directly at the reflected image of the flame. In such a view the retina appears to be much darker, grayish-yellow, and without any admixture with red; also, no traces of any capillary vessels are visible upon it. In observing this site, however, one is very much disturbed by the corneal images, which are situated exactly in the center of the field of vision, whereas when more lateral portions of the retina are examined these reflexes are situated somewhat more to the side.

After one learns to recognize the characteristics of the retina in the normal eye, I have no doubt that it will be possible to diagnose all the pathologic conditions of the retina by visual observation, as is done in examination of other transparent parts, such as the cornea. Engorgement of the vessels or varicosities of the vessels can easily be perceived. Exudates in the substance of the retina, or between the retina and the pigment layer, can be recognized by their light appearance against the dark background, similar to what can be seen in corresponding lesions in the cornea. If they are situated partly in front of the retina, the blood vessels will be hidden as by a veil. In this respect, I recall that, according to Brücke, the living retina is almost as transparent as the other ocular media. In our investigations, except for the vessels, the retina has become visible only because it is strongly illuminated by the bright light which is concentrated by the ocular media on the dark background of the pigment layer. Fibrinous exudates, which are much less transparent than the ocular media, must therefore considerably increase the reflex if they are situated in the fundus of the eye. I also believe that opacities of the vitreous body will be recognized much more readily and exactly, partly through illumination by means of the reflecting glass plate and partly by examination through the ophthalmoscope. It is easily possible to estimate the extent of the opacity by means of the degree of blurring of the retinal vessels and of the image of the flame. If scintillating particles have become detached from such an opacity, these also may be perceived readily. In short, I believe I do not exaggerate when I anticipate that all those changes in the vitreous body and the retina previously noted in cadavers will be recognized in the living eye. This fact appears to offer the greatest impetus to development of the pathologic study of these structures.

Finally, for several physiologic reasons, it is of interest to investigate the accuracy with which the eye forms images. For this purpose, it is best to employ a thread which is stretched out horizontally before the flame. Its image remains single, while vertical threads are multiplied by the numerous reflections.

Next, there is an opportunity to appreciate through inspection that the varying accommodation of the eye actually depends upon changes in the refractive media. One should fixate an object which is about as far removed from the observed eye as is the thread from the flame. The observer then can see equally clearly the elements of the retina and the image of the thread. If, then, the thread is brought either nearer to the eye or farther from it, it becomes blurred or disappears entirely

from the retinal image, while the retinal portions remain clear. It is evident from this that retinal images of variously distant objects actually are not equally distinct. Then the thread is again placed in such position that it is seen distinctly in the retinal image simultaneously with the vessels, and the subject fixates a point which is either much farther or much nearer than that which was formerly employed. Immediately the retina and the image of the flame become blurred and indistinct.

It should be noted that no clear image is projected upon the white surface of the optic nerve, even when it appears to be sharply defined on the immediately adjacent portions of the retina. Since the observer can perceive that in persons who have tiny vessels coursing over the cross section of the optic nerve these are seen just as clearly as are those in the adjacent retina, the blurring of the image of the flame cannot originate from any displacement of the surface of the optic nerve from the level of the retina. I believe, rather, that the cause of this is the transparent nature of the substance of the optic nerve.

Moreover, it is possible, when it is necessary to do so, easily to determine objectively the presence and the degree of myopia or hyperopia of the observed eye. The observer should first examine a normal eye. He should allow this eye to fixate objects at various distances and should note which concave lenses are needed at the various stages of accommodation of the eye. Then, in investigating another eye, he can determine, by the strength of the concave lens needed to give a clear view of the retina, the state of accommodation of the subject's eye. The observer is thus entirely independent of the statements of the subject, since he himself can see, as though with the other's eye, the refractive media of this eye. In this way, for example, I was able to examine a completely amaurotic eye and determine that this eye was highly myopic as well. This settled a question, which was of great importance in this case, as to whether certain earlier difficulties with vision, as recounted by the patient, could be ascribed to myopia or to beginning amblyopia.

These investigations led me to an important physiologic deduction. The isolated cross section of the optic nerve evidently is so transparent that light falling upon it can penetrate deep into the substance of the fibers, inasmuch as at times the tortuous loops of the central artery and central vein can be seen shimmering through the substance of the nerve. If the image of the flame is cast upon the site of entry of the optic nerve, all the nerve fibers, or at least a very large portion of them, are exposed to more or less intense light, and yet apparently no light is perceived. If it were to be perceived, then the entire portion of the visual field corresponding to this site would have to be illuminated. This, however, is not true, since even less light is perceived here than when the image is cast upon some other situation in the retina. We must, therefore, conclude that the fibers of the optic nerve are insensitive to objective light (ethereal vibration), although every other kind of stimulation is perceived as subjective light. This is an apparent paradox, which, of course, has its origin only in the ambiguity of the word "light," and is far from being an actual contradiction. The vibrations of the ether which we call "light," as well as every other mechanical or electrical stimulus, produces a sensation on striking the retina which we also perceive as "light." However, in spite of the fact that the retina is protected against pressure and electrical currents and is exposed to the action of the vibrations of the ether, being much oftener struck and stimulated by the latter than by the former, one must not conclude that light is a more efficient stimulant

of the retina and of the elements of the optic nerve than are other kinds of stimulation. It is not difficult to make the assumption that all stimuli which are able to act on the visual nerve system produce sensations of light, but that the vibrations of the ether are able to act only on the retina. This similar situation may be noted in the reaction of the nerves of touch to warmth and cold. In this case as well there is a different response in the peripheral ramifications than there is in the trunk. In the latter it appears that slight variations of temperature do not stimulate, whereas greater variations, which certainly succeed in stimulating, give no thermal sensations. Furthermore, it is possible to conclude that in the retina it is the cellular elements which are sensitive to light, and not the nerves which radiate over the inner surface.

If it were otherwise, then light which impinges on one spot on the retina would not only stimulate all the nerves which terminate in this location, but also those which course out farther into the periphery. This would, then, cause every illuminated point to possess a bright glare, widening out to the periphery of the visual field, but this is not the case. We are able, therefore, to postulate further that the continuations of the visual nerve fibers in the retina are insensitive to light. This leaves only the ganglion cells and the nuclear-like structures in the retina on which the vibrations of the ether can act as a stimulant.

APPENDIX

Derivation of Formula for Quantity of Light Which Is Reflected from Several Glass Plates (page 571).—If this formula is correct for n reflecting surfaces, it can be shown that it is also correct for $(n + 1)$ such surfaces. Since it holds good when $n = 1$ and $n = 2$, it must also be true for any desired value for n.

Let p represent the quantity of light which is reflected from a reflecting surface at the given angle of incidence when the amount of light polarized perpendicular to the incident surface is 1; and the quantity reflected from n surfaces, P_n, and that reflected from $(n + 1)$ surfaces as $P_{(n+1)}$. It can be shown that if $P_n = \frac{np}{1 + (n - 1)p}$ (1) then the equation which is obtained by substituting $n + 1$ for n also is correct:

$$P_{n+1} = \frac{(n + 1)p}{1 + np} \tag{2}$$

For the sake of a better description, let us assume that the system of n reflecting surfaces lies horizontal and light strikes it from above. The $(n + 1)$th surfaces can be added on below. That quantity of light which passes downward from the lowest n surface of the compound system to the $(n + 1)$th surface, we may call x, and that which is reflected back to the system of n surfaces from the $(n + 1)$th surface, y. The quantity, x, is composed partly of the portion of the incident light which has passed through the system of n surfaces and partly from that part of y which is reflected from this system.

Therefore, $X = 1 - P_n + y P_n$. (3)

The quantity, y, originates from that portion of x which is reflected from the $(n + 1)$th surface.

Hence, $y = xp$. (4)

The quantity, $P_{(n+1)}$, which passes upward from the uppermost surface originates partly from that portion of the incident light which is reflected from the system of

n surfaces and partly from the portion of y which passes through this system.

Therefore, also $P_{n+1} = P_n + y\,(1 - P_n)$. (5)

If x and y are eliminated from equations 3, 4, and 5,

$$P_{n+1} = P_n + \frac{p\,[1 - P_n]^2}{1 - pP_n}. \quad (6)$$

If, in equation 6, the value of $P_{(n)}$ is obtained from equation 1, after the necessary reduction, equation 2 is obtained, the correctness of which was to be proved.

For *one* reflecting surface, $P_{(1)} = p$. Equation 1, which is to be tested, gives the same value.

For two reflecting surfaces, we obtain the value $P_{(2)}$ without employing equation 1 or 2 if, in the derivation of equation 6, we assume that $n = 1$ and $P_{(n)} = p$.

Equation 6 then becomes $P_2 = p + \frac{p\,(1-p)^2}{1-p^2} = \frac{2p}{1+p}$

giving the same value as equation 1.

Since the latter is correct for $n = 1$ and $n = 2$, it follows from the previous proofs that it is also correct for $n = 3$; and if it is correct for $n = 3$, it is also correct for $n = 4$, and so on, ad infinitum.

This is equally applicable to light polarized parallel to the incident surface.

If we designate the quantity of incident light as equal to $\frac{1}{2}\,J$ and $p = \frac{2P}{J}$, and then designate as II what we have here called $P_{(n)}$, we obtain the formula

$$II = \frac{nP}{J + 2\,(n-1)\,P} J.$$

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

ACUTE GLAUCOMA SIMULATING ACUTE IRITIS

There is usually no difficulty in distinguishing an attack of acute primary glaucoma from acute iritis. However, if the patient is first seen soon after the hypertensive phase has spontaneously subsided, the condition may be easily mistaken for acute iritis. This occurred in the case to be reported.

P. L., a white woman aged 71, was seen in the outpatient department of the Massachusetts Eye and Ear Infirmary, complaining of a foreign-body sensation in the left eye, along with photophobia of two weeks' duration. These complaints were preceded by severe, sudden pain in the left eye, which had gradually abated in the previous week. The right eye had been injured 45 yr. ago and was enucleated 20 yr. later.

Examination of the eye revealed the following condition: The right socket showed nothing abnormal. Examination of the left eye was made difficult because of severe photophobia. Vision was 20/70 and was unimproved with the pinhole disk. There were moderate mixed injection of the globe and considerable edema of the corneal epithelium. This edema was largely limited to the area of the palpebral fissure; there were some medium-sized bullae in this location. Folds in Descemet's membrane were noted. It was difficult to examine the anterior chamber, owing to the corneal edema. The pupil was 6 mm. in diameter, round, regular, and fixed. The tension was 18 mm. (Souter). A red reflex only could be obtained from the fundus.

A few days after the patient's admission to the hospital the cornea had cleared without treatment, permitting a more detailed examination. A moderate flare and a moderate number of cells could now be seen. There were no keratic precipitates. The anterior chamber was of average depth axially. Fibrinous deposits were noted on the lens capsule. The tension was 21 mm. Hg (Schiøtz).

In view of these findings, it was felt that the patient had an iritis toxic enough to affect the permeability of the endothelium, accounting for the corneal edema. The endothelium could not be seen very clearly with the slit lamp, but no gross disturbance could be made out.

The patient was given atropine sulfate 1% three times a day and cortisone (5 mg. per cubic centimeter) drops hourly. The eye became white; the cornea cleared within a few days; the flare and cells disappeared, and the tension remained normal. The patient was discharged four days after admission, free of complaints. She was seen repeatedly in the outpatient department during the next three weeks. Treatment consisted of instillation of scopolamine hydrobromide (0.2%) drops three times a day. She remained asymptomatic, and the eye was essentially normal during this period.

Three days after stopping use of the scopolamine drops, the patient returned complaining of misty vision and severe, sudden pain, of 24-hr. duration. She was also aware of severe photophobia and tearing.

Examination at this time showed that vision in the left eye was reduced to counting fingers at 2 ft. (60 cm.). There were considerable edema of the left upper lid, intense injection of the globe, and severe bullous keratopathy. After the cornea had partially been cleared with glycerin, it was noted that the anterior chamber was of average depth axially, but at the periphery the iris seemed to be almost in contact with the posterior surface of the cornea, suggesting a very narrow angle. Gonioscopic examination was attempted but was unsatisfactory,

owing to the corneal haze and the constant movement of the eye. The pupil was 7 mm. in diameter and was fixed. Details of the anterior chamber were difficult to make out, owing to the corneal edema, but some flare was noted. There were no keratic precipitates. Only a red reflex could be seen from the fundus. The tension was more than 87 mm. Hg (Schiøtz). After a few-hours' intensive treatment with miotics, the tension dropped to within the normal range, although the pupil remained semidilated.

The next day a basal iridectomy was performed, and after complete absorption of a moderate hyphema, the tension leveled off to normal limits, where it has since remained without use of drops. The eye has been quiet, free of redness, and comfortable. Gonioscopic examination a few weeks after operation revealed a very narrow angle. The optic disk and visual field were normal. Vision was correctable to 20/20.

In retrospect, it seems clear that the patient was in the postacute phase of glaucoma when she was first seen. However, because of the essentially normal tension and the average depth of the chamber, the diagnosis of acute glaucoma was not seriously considered. Undue emphasis was placed on the flare and cells, leading to the diagnosis of acute iritis.

The fulminating onset of pain, together with a fixed, semidilated pupil and severe loss of vision, even in the absence of elevated tension, strongly suggests acute glaucoma. The pain of iritis tends to build up gradually, and the pupil tends to be small. The presence of a flare and cells should not in any way shift the emphasis from acute glaucoma to iritis, inasmuch as these are common to both conditions. It should also be noted that an anterior chamber with average axial depth does not rule out the possibility of a narrow angle.

It is noteworthy that the patient's condition continued to improve while she was using atropine and scopolamine drops and that it flared up with her last attack a few days after she discontinued use of the latter.

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Dr. Paul A. Chandler aided in the interpretation of this case.

Annual Reviews

NEURO-OPHTHALMOLOGY

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RECENT publications pertaining to neuro-ophthalmology, while they resemble those of years past, especially indicate advances in the diagnosis and the management of aneurysms, a renewed interest in disturbances in movements of the eye, and continued struggle with the problem of headache.

PERIMETRY

The reader who is a novice in ophthalmologic procedures or who is not satisfied with his perimetry can do no better than read and apply in his own practice the concise list of suggestions offered by Darley,[1] perimetrist at the Manhattan Eye, Ear, and Throat Hospital. She offers no short cuts; yet experienced perimetrists will agree that her meticulous technique saves time in the end and that it gives the examiner who uses it confidence that his work is accurate and reliable. In teaching institutions, students would benefit if her suggestions could be posted over the perimeter. Her list does not require reproduction here.

Chamlin, writing with Davidoff,[2] once again calls attention to the value of the 1-mm. white bead, used on a tangent screen at 2 m. His repeated emphasis on the need for small targets and painstaking technique is a valued contribution to ophthalmology and, it is hoped, will be heeded eventually by everyone concerned with perimetry. In this paper the procedure is recommended for the study of patients with lesions at the optic chiasm. The authors' experience confirms the observations of Traquair that the 1/2000 field is always involved as early as, and usually before, the peripheral field. When improvement has taken place after operation or x-ray therapy, the 1/2000 field is the last to fill out. They demonstrate, too, on charts of the visual fields of a selected series of their patients, that the 1/2000 field is always involved as much as, and usually more than, the peripheral field. They furnish several illustrations of full peripheral fields associated with temporal depression of the 1/2000 field, and also illustrations of incomplete temporal hemianopsia of the peripheral field with complete temporal hemianopsia of the 1/2000 field. In their experience red-colored targets have been unsatisfactory for demonstrating the extent of a particular isopter. Because the target seems to undergo a transition from one color to another as it is carried in from the periphery, the patient is at loss to say when the object first appears true red. Reduced acuity of central vision, as measured on the Snellen chart, is considered by Chamlin and Davidoff [2] a late indication of interference at the chiasm, and this is preceded by involvement of the 1/2000 field.

From the Section of Ophthalmology, Mayo Clinic.

1. Darley, L. H.: Visual-Field Testing: Suggestions on Technique, Am. J. Ophth. **33**:1428-1431 (Sept.) 1950.

2. Chamlin, M., and Davidoff, L. M.: The 1/2000 Field in Chiasmal Interference, Arch. Ophth. **44**:53-70 (July) 1950.

On the basis of clinical observations, but admittedly without corroborative anatomic studies, the same authors offer their own concept of the distribution of the crossed fibers in the optic chiasm. They place the macular fibers at the posterior edge, the paramacular fibers immediately in front of them, fibers from the intermediate field (10 to 25 degrees) on the ventral surface of the chiasm, and peripheral fibers on its dorsal aspect. From a clinical point of view this suggestion is plausible, but clinical material alone scarcely can be expected to solve the problem of the arrangement of fibers within the chiasm.

Another method of examining the central field for minute changes is proposed by Renfrew.[3] He determined perception of form at intervals of 5 degrees from the point of fixation to 25 degrees on a black tangent screen at 2 m. His test targets were black cards 2½ in. (6.4 cm.) square; on one side strips of white paper were arranged to form square figures; on the opposite side the same amount of white paper was in a jumble. He reports that there is much individual variation in extrafoveal perception of form, and that his method rarely gives additional information when the ordinary perimetric fields are affected. He guesses, however, that his proposed method may reveal defects earlier than the ordinary studies of perimetric fields will.

Exploration of the visual fields by means of a technique which utilizes determinations of flicker-fusion frequency is the subject of three more papers by Miles.[4] Three previous papers on the same subject by the same author fell within the scope of this review last year. At that time this reviewer expressed confidence that Miles would contribute a practical, sensitive technique to clinical perimetry. The last three papers have not strengthened this confidence.

In a discussion on technique and interpretation, Miles cites the experience of seven other clinicians with flicker-fusion frequency fields and describes two methods of his own, one employing a 5-cm. illuminated disk for use on a 50-cm. perimeter, and the other employing a 10-foot-candle lamp, of unspecified size, placed on the end of a wand for use at a 1-m. tangent screen. Charts are shown which indicate the results of the latter method in cases of glaucoma, tumor of the optic nerve, optic neuritis, and pituitary adenoma. Areas of reduced flicker-fusion frequency correspond in a general way to the defects expected through ordinary testing, but such charts are not shown.

In the second article, Miles compares in 47 cases the flicker-fusion fields with those obtained by standard methods, that is, for 3/330 white on the perimeter and for 1/1000 white on the tangent screen. Three illustrative cases are presented, in one of which the results were comparable and in two of which defects obtained by flicker fusion were more intense than those obtained by standard techniques. His technique differs from that described in his previous papers, for in this study he has employed a flickering light, 3 to 4 cm. in diameter and a flash duration of 10 μsec. attached to the end of a wand, and a perimeter constructed of a wire frame

3. Renfrew, S.: The Regional Variations of Extrafoveal Pereeption of Form in the Central Visual Fields (Photopic Vision), with Special Reference to Lesions of Visual Pathways, Brit. J. Ophth. **34**:577-593 (Oct.) 1950.

4. Miles, P. W.: Flicker Fusion Fields: II. Technique and Interpretation, Am. J. Ophth. **33**:1069-1077 (July) 1950; Testing Visual Fields by Flicker Fusion, Arch. Neurol. & Psychiat. **65**:39-47 (Jan.) 1951; Flicker Fusion Fields: IV. Neuro-Ophthalmic Lesions, Am. J. Ophth. **34**:51-56 (May, Pt. II) 1951.

with a radius of 1 m. and an arc extending out only 30 degrees. The flicker-fusion fields were considerably superior to standard fields in 28 of the 47 cases and slightly superior in 11 cases. In 23 of the cases flicker-fusion fields showed changes of localizing value when standard fields showed nothing. In no case was the flicker-fusion field inferior to the standard field. These statements would be more convincing had there not appeared on the same page the statement, "During pregnancy there is regularly a bitemporal slant, due to physiological enlargement of the pituitary gland." In the past this statement has usually been made by perimetrists who found what they wished or expected to find.

In Miles's third article of the past year the same instrument and technique are described except that the duration of each flash was 40 μsec. This may be a typographical error, for the 47 cases considered appear to be the same as those described in the second article. The wording and some of the illustrations are different, however.

The three most important tumors at the optic chiasm are discussed by Okonek.[5] He points out that adenomas of the pituitary gland, both chromophil and chromophobe, are intrasellar and are sensitive to x-rays. If visual loss is associated, operation is indicated; if there is no loss of vision, x-ray therapy suffices. Craniopharyngioma arises from misplaced cells of Rathke's pouch, is suprasellar and cystic, generally contains calcium, visible roentgenographically, and may be responsible for increased intracranial pressure. It is not sensitive to x-ray therapy, and usually complete surgical extirpation is not possible. Suprasellar meningioma extends upward and posteriorly, is richly vascularized, and is resistant to x-ray therapy. Total extirpation, when feasible, effects a cure.

Tumors of the pituitary gland, pineal body, and third ventricle are considered by Pennybacker,[6] in a didactic, well-illustrated paper. He points out that chromophobe adenomas of the pituitary gland are twice as common as chromophil adenomas. In the former, loss of vision is the most frequent presenting symptom. In the latter, symptoms of acromegaly are present, and there may be a distressing, bursting type of headache, the cause of which has never been explained satisfactorily, but which usually responds to x-ray therapy. Meningioma arising in the region may have as its sole symptom loss of vision. With aneurysm there is usually considerable pain and headache. Craniopharyngioma (or adamantinoma) is not favorable for surgical treatment, for it adheres to neighboring structures, tends to recur, and is not radiosensitive. Glioma growing in the wall of the third ventricle cannot be removed and must be treated with radiation. Tumors of the pineal body obstruct circulation of cerebrospinal fluid, produce headache and papilledema, and press on the superior colliculi, causing paralysis of upward movement of the eyes and immobility of the pupils to stimulation by light, with preservation of reaction on convergence.

Gartner[7] describes the eyes in a case of pituitary tumor in which necropsy was performed. Shortly before the patient's death, the right eye was almost blind,

5. Okonek, G.: Das Syndrom der Sehnervenkreuzung: Bemerkungen zur Differentialdiagnose, Therapie und Prognose der sellären und suprasellären Geschwülste, Klin. Monatsbl. Augenh. **116**:113-130, 1950.

6. Pennybacker, J.: Pituitary, Pineal and Third Ventricle Tumors, Post-Grad. M. J. **26**:141-155 (March) 1950.

7. Gartner, S.: Ocular Pathology in the Chiasmal Syndrome, Am. J. Ophth. **34**:593-596 (April) 1951.

and the left possessed vision in only the nasal half-field. In microscopic sections, the right eye exhibited atrophy of the ganglion cells throughout the retina; in the left eye, however, there was a vertical dividing line through the macula, with normal ganglion cells on the temporal side and atrophy of the ganglion cells on the nasal side, accompanied with atrophy of the nerve-fiber layer. The other layers of the retina appeared normal. Although these findings are what might have been predicted, this reviewer is not aware of a similar study.

Misleading defects in visual fields associated with intracranial tumor form the subject matter of a paper by Klingler and Condrau.[8] After referring to pertinent literature, these authors present four cases of their own in which diagnosis had proved difficult because the field defects gave false information. In the first case a meningioma of the falx in the parietal region was responsible for a central scotoma in the left eye. In the second case an astrocytoma of the cerebellum caused bilateral central scotoma. In both cases increased intracranial pressure produced the prechiasmal type of field defect. In the other two cases meningioma of the falx was associated with homonymous hemianopsia, which was found to be a distance symptom on completion of examinations.

Psychogenic changes in the field of vision associated with tumors of the frontal lobe of the brain are described by Gogela and Rucker[9] in a report of 18 cases. The defect in the field usually took the form of generalized contraction or of a spiral. In a few cases the field returned to normal after removal of the tumor; in other cases, after decompression alone. In some, extensive removal of tumor tissue failed to effect improvement. The authors warn that the finding of a psychogenic defect in the field of vision does not eliminate the possibility of an organic lesion.

Yasuna[10] reports his experience with hysterical amblyopia in 19 children and young adults. The amblyopia was bilateral in 80%. He comments on the importance of study of the peripheral fields in establishing a diagnosis—the steep borders of the defects and the amazing constancy of the tubular field, regardless of the distance at which it is tested.

Amaurosis fugax and amaurosis fulminans are considered by Behrman.[11] Under the former designation he includes the blackout which occurs when cerebral blood pressure falls below intraocular pressure and the transient visual loss associated with migraine, hypertension, and papilledema. The more permanent amaurosis fulminans may be due to closure of both posterior cerebral arteries; to closure of arteries in the optic nerves, as in temporal arteritis; tumors at the sella turcica; optic neuritis, or basal meningitis. Finally, he mentions briefly the cases of cerebrovascular accidents which result in temporary blindness and then partial recovery, ending in homonymous hemianopsia. He does not think that transient occlusion of the cerebral arteries on both sides accounts for the phenomenon and states that there may be temporary activation of a suppressor strip near the striate cortex.

8. Klingler, M., and Condrau, G.: Lokalisatorisch irreführende Gesichtsfeldsymptome bei Hirntumoren, Ophthalmologica **120**:270-285 (Nov.) 1950.

9. Gogela, L. J., and Rucker, C. W.: Psychogenic Changes in Field of Vision, Associated with Tumors of the Frontal Lobe of the Brain, Am. J. Ophth. **34**:185-188 (Feb.) 1951.

10. Yasuna, E. R.: Hysterical Amblyopia in Children and Young Adults, A. M. A. Arch. Ophth. **45**:70-76 (Jan.) 1951.

11. Behrman, S.: Amaurosis Fugax et Amaurosis Fulminans, A. M. A. Arch. Ophth. **45**:458-467 (April) 1951.

Right or wrong, this is the first plausible explanation that has come to the attention of this reviewer. He has never been able to explain to his own satisfaction why, in some cases of cerebral infarct, complete blindness should precede by a few hours or days the homonymous hemianopsia.

OPTIC NERVES

In a comprehensive statistical survey of the ocular manifestations of multiple sclerosis, Marshall [12] reviews cases observed at the University of Michigan Hospital between the years 1934 and 1948. Of 822 patients with multiple sclerosis, 91% showed ocular signs at some time during the course of the disease. Sixteen per cent showed optic nerve atrophy in one or both eyes, and 1.3%, papillitis. Forty per cent had nystagmus, and in most instances it remained, once it appeared. Diplopia occurred at some time during the course of the disease in 30% and was the first symptom in 5%. Retrobulbar neuritis occurred at some time in 30% and was the first symptom in 13%.

Marshall also studied a series of 322 patients with optic and retrobulbar neuritis. Multiple sclerosis was definitely present in 13% and was suspected in 17%, a total of 30%. These observations coincide with the findings of other investigators, that the most frequent of many possible causes is multiple sclerosis. Of this group of patients, 73% were under observation for less than six months, and only a few for more than five years.

Another review of the ocular manifestations of multiple sclerosis is presented by Yaskin, Spaeth, and Vernlund,[13] who studied 100 patients with multiple sclerosis admitted to their hospital services. In general, their findings resemble those of Marshall. Of their 100 patients, 56 had ocular manifestations of the disease, and 27 gave these as the presenting symptoms. Changes in the optic disks were visible in 51 patients. Nystagmus was present in 34. Paralysis of extraocular muscles was present in 12 and was the initial symptom in seven. Retrobulbar neuritis occurred at some time in 31 and was the initial symptom in 14. It was possible to follow 20 patients who had primary ocular symptoms for a number of years. In four of these, other symptoms of multiple sclerosis did not develop until 10 to 14 years after the primary ocular symptoms.

Neither of these studies answers the controversial question of how many patients who have an initial episode of acute retrobulbar neuritis will eventually become afflicted with multiple sclerosis. A follow-up study of a significantly large series of patients over a 25-year period is sorely needed.

Walsh and Hedges [14] report on a study of the relation of hemorrhage in the sheath of the optic nerve to intracranial hemorrhage. In six cases of spontaneous intracranial subarachnoid hemorrhage, they obtained at necropsy the optic nerves and canals, and they also had available for study 180 specimens of the posterior segment of the eyeball and attached end of the optic nerve, in the sheath of which blood was present. They demonstrated that hemorrhage in the optic nerve sheath

12. Marshall, D.: Ocular Manifestations of Multiple Sclerosis and Relationship to Retrobulbar Neuritis, Tr. Am. Ophth. Soc. **48**:487-525, 1950.

13. Yaskin, J. C.; Spaeth, E. B., and Vernlund, R. J.: Ocular Manifestations of 100 Consecutive Cases of Multiple Sclerosis, Am. J. Ophth. **34**:687-697 (May, Pt. I) 1951.

14. Walsh, F. B., and Hedges, T. R., Jr.: Optic Nerve Sheath Hemorrhage, Am. J. Ophth. **34**:509-527 (April) 1951.

does not originate as a result of forward passage of blood from the intracranial meningeal spaces, for there is little, if any, passage forward of blood from these spaces through the optic canal. Concomitant with the hemorrhages in the sheath, they observed small hemorrhages into the third nerve in its course through the cavernous sinus, as well as into the chiasm and the intracanalicular portion of the optic nerve, and preretinal bleeding from ruptured central retinal veins. These, like hemorrhages in the sheath of the optic nerve, followed increased venous pressure transmitted from the cranial cavity to the orbital veins. The authors conclude that hemorrhages in the sheath of the optic nerve originate in rupture of veins in the dural sheath of the nerve. The degree and extent of venous ruptures are dependent on the rapidity of onset and magnitude of elevation of venous pressure in the brain and orbit.

A few accounts of tumors of the optic nerve appear in recent publications. Cohen [15] reports six cases of such tumors: gliomas in four young girls and hemangioma and meningioma each in an adult. One of the girls exhibited pigmented spots over the body, as seen in neurofibromatosis, but none of the others showed the condition. In three of the four cases of glioma the tumor involved the chiasm; in only one case was it limited to the optic nerve. Progress of this disease is slow and may be retarded further by roentgen irradiation.

A single case of glioma of the optic nerve presented by Mitchell [16] illustrates some of the usual features of this tumor. The patient was a boy 3 years old. The parents had noticed increasing prominence of the right eye. Examination disclosed proptosis of 4 mm. and 6 D. of papilledema in the affected eye. On roentgenograms, the right optic canal measured 6 mm., and the left, 5 mm. There was no evidence of neurofibromatosis. The preoperative diagnosis was glioma of the optic nerve, and this was confirmed at operation, when the tumor and optic nerve and globe were removed by transfrontal craniotomy.

Another case is reported by Bucy, Russell, and Whitsell.[17] Their patient, a boy 10 years old, had reduction in vision and proptosis of 3.5 mm. of the left eye, without limitation of rotation of the globe; the fundus was normal except for fulness of the retinal veins. Roentgenograms of the skull, orbits, and optic canals revealed no abnormalities; there was no evidence of neurofibromatosis. A glioma of the optic nerve was removed by transfrontal craniotomy. The authors recommend formation of a frontal flap and unroofing of the orbit as offering the best approach to the removal of such tumors. The reviewer concurs.

Some of the difficulties in the diagnosis of lesions affecting the optic nerves are brought out by Blazar and Scheie [18] in an article on pseudoglaucoma. By this term they imply cupping of the optic disks, optic nerve atrophy, and arcuate defects in the fields, without raised intraocular pressure, yet with an adequate explanation for the defects. These authors have been impressed with the importance of careful

15. Cohen, I.: Tumors of the Intracranial Portion of the Optic Nerve, J. Mt. Sinai Hosp. **17**:738-745 (March-April) 1951.

16. Mitchell, R. M.: Glioma of the Optic Nerve: Report of a Case Cured by Operation, New Zealand M. J. **49**:686-688 (Dec.) 1950.

17. Bucy, P. C.; Russell, J. R., and Whitsell, F. M.: Surgical Treatment of Tumors of the Optic Nerve: Report of a Case, Arch. Ophth. **44**:411-418 (Sept.) 1950.

18. Blazar, H. A., and Scheie, H. G.: Pseudoglaucoma, Arch. Ophth. **44**:499-513 (Oct.) 1950.

study of those patients who seem to have glaucoma but who do not have an increase in intraocular tension, for a variety of lesions of the optic nerve can produce nerve-fiber-bundle defects. After reviewing the literature, the authors present four cases of their own—one of pituitary tumor, one of congenital colobomas of the optic nerves, one of syphilitic atrophy of the optic nerve, and one of calcification of the internal carotid arteries. The first two patients had been treated for several years on the false assumption that the visual loss was due to glaucoma.

During the past year an exhaustive monograph on retrobulbar optic neuropathy was published by Mata Lopez,[19] in Spanish.

ANEURYSMS

Aneurysms at the circle of Willis continue to offer perplexing problems. Their management is still unsatisfactory and discouraging. Some reason for optimism lies in advances being made in diagnostic methods and in the greater awareness of aneurysms on the part of ophthalmologists. Many aneurysms produce signs that are evident in the eyes. When their surgical treatment loses its gloomy aspect, perhaps ophthalmologists will be more tempted to write up cases that come to their attention. Currently, all too few such cases find their way into the ophthalmologic literature.

Meadows [20] reviews features of aneurysms of the intracranial portion of the internal carotid artery. He notes that in the first part of its course the artery lies within the cavernous sinus, and in the second part of its course, after piercing the dura and leaving the sinus, it follows the inner side of the anterior clinoid process and then terminates in the middle and anterior cerebral arteries.

The intracavernous (infraclinoid) portion lies in close association with the oculomotor nerve, the first and second divisions of the trigeminal nerve, and the ocular sympathetic fibers. Aneurysm of this portion of the vessel, as it expands, causes intense pain in the region of distribution of the first division of the trigeminal nerve, and as it extends posteriorly may involve the second, or even the third, division. Pain is followed by involvement of the third, fourth, or sixth cranial nerve. Should an aneurysm in this location rupture spontaneously or as a sequel of head injury, the initial symptom is a beating noise in the head, which may be heard by the examiner as a bruit. This is followed by exophthalmos, which usually pulsates and may be unilateral or bilateral. Congestion of the conjunctival vessels is a constant feature. The appearance of the fundi is variable; it may be normal, or there may be evidence of venous thrombosis, papilledema, or optic nerve atrophy.

Aneurysm arising from the terminal, extracavernous (supraclinoid) portion of the carotid artery is particularly liable to give rise to paralysis of the third cranial nerve. There may be additional involvement of the ophthalmic branch of the trigeminal nerve, or of the optic nerve or chiasm, with pain and loss of vision. Rupture of an aneurysm in this location gives rise to subarachnoid hemorrhage; the mortality following rupture is about 50%.

Mooney [21] gives details of 16 cases of aneurysm of the internal carotid artery. Pain was present in all of them (an unusual feature of tumors in the region). In

19. Mata Lopez, P.: Neuropatía óptica retrobulbar, Arch. soc. oftal. hispano-am. **10**:653-741 (July) 1950.

20. Meadows, S. P.: Aneurysms of the Internal Carotid Artery, Tr. Ophth. Soc. U. Kingdom **69**:137-155, 1949.

21. Mooney, A. J.: On the Diagnosis of Certain Intracranial Vascular Lesions, Tr. Ophth. Soc. U. Kingdom **69**:621-646, 1949.

13 cases there was third-nerve paralysis; in four, papilledema, and in three, a defect in the field of vision. In addition, he presents two cases of thrombosis of the left internal carotid artery, with hemiparesis in each case, visual loss in the left eye in one case, and blindness in both eyes in the other. He states that lesions of the internal carotid artery may be the cause of unexplained blindness in some cases and recommends angiography as a useful aid in the diagnosis of lesions of the internal carotid artery.

His thesis bears emphasis: Severe frontal pain with third nerve paralysis, especially in middle-aged persons, should make one suspect aneurysm of the internal carotid artery.

Sugar, Webster, and Gurdjian [22] report three cases of spontaneous thrombosis of the carotid artery. The ages of their patients were 24, 63, and 26 years. In the two younger patients there was sudden onset of hemiparesis and blindness of one eye, due to closure of the central retinal artery. In the oldest patient visual loss was attributed to involvement of nutrient arteries of the optic nerve, and the only other disturbance was twitching of the side of the face. In all cases pulsation was absent in the carotid arteries, and organized thrombi were demonstrated surgically.

Cerebral angiography has become an essential diagnostic procedure in neurologic disease, and, largely as a result of it, neurosurgeons have been able to deal more effectively with some of the cerebral vascular disorders. Bull,[23] in a splendid review of its clinical application, points out that in recent years the direct percutaneous puncture of the vessel has been performed and an "almost benign" contrast substance ("diodone" [the diethanolamine salt of 3,5-diiodo-4-oxo-1,4-pyridineacetic acid]) has been used. The author reports three deaths in 1,000 cases but adds that he has seen fits, hemiplegia, and coma, without disclosing their incidence or further details. Cerebral angiography he finds useful in the diagnosis of spontaneous aneurysms, either congenital or arteriosclerotic. The former are pedunculated, the latter fusiform; either may burst or may erode bone. In cases of chronic subdural hematoma arteriography provides a pathognomonic picture in the anteroposterior position, wherein it shows the middle cerebral vessels displaced medially from the inner table of the skull. Tumors may be localized by angiography, but in general ventriculography is more accurate.

Specific complications of arteriography as they affect the eye are reported by Falls and associates,[24] who made observations on 80 consecutive patients. They noted petechial hemorrhages in the conjunctiva of 65 patients and hemorrhages in the retina of 20. Many of the hemorrhagic areas in the retina presented white centers, and in some cases cotton-wool exudates were present also. In 35 of the patients there were petechiae in the skin of the eyelids. In one patient optic neuritis, with eventual complete loss of vision, ensued. One death, secondary to thrombosis of the internal carotid artery, occurred. The authors investigated the incidence of

22. Sugar, H. S.; Webster, J. E., and Gurdjian, E. S.: Ophthalmologic Findings in Spontaneous Thrombosis of the Carotid Arteries, Arch. Ophth. **44**:823-832 (Dec.) 1950.

23. Bull, J. W. D.: Cerebral Angiography, Post-Grad. M. J. **26**:156-165 (March) 1950.

24. Falls, H. F.; Bassett, R. C., and Lamberts, A. E.: Ocular Complications Encountered in Intracranial Arteriography, A. M. A. Arch. Ophth. **45**:623-626 (June) 1951.

severe systemic complications by reviewing the records of 457 patients who had undergone intracranial arteriography and found that four had become seriously comatose, six had suffered hemiplegia, and six had experienced convulsions.

Arteriography is an invaluable diagnostic aid in many instances, but is not to be undertaken lightly.

PUPILS

Localization of lesions causing Horner's syndrome is accomplished by Jaffe [25] through the use of drugs instilled in the eyes and through evaluation of signs attributable to involvement of neighboring structures. He first instils cocaine (4% solution) in each eye; he makes three applications, with an interval of three minutes between them. The drug fails to dilate a Horner pupil if the lesion is in the second or third neuron, or between the center of Budge, in the cord, and the dilator fibers of the iris. Forty-five minutes after the cocaine test he instils epinephrine hydrochloride (1:1,000 solution) in each eye; he again uses three applications, with an interval of three minutes between them. When the lesion is in the third neuron, between the superior cervical ganglion and the dilator fibers in the iris, there is good dilation of the pupil. When the lesion is in the second neuron, the dilating effect is small; when the lesion is in the first neuron, between the hypothalamus and the center of Budge, there is no effect. The normal pupil, of course, is not affected by epinephrine. Homatropine dilates a Horner pupil relatively little, no matter where the site of the lesion.

Neighboring structures may give signs helpful in determining the site of the lesion. Lesions of the first neuron, in the brain stem and the cervical portion of the cord, give rise to neurologic signs according to their location. The accompanying ptosis may be slight. Involvement of the second neuron, in the upper part of the thorax or the lower part of the neck, may be accompanied with signs suggestive of cervical rib, tuberculosis or cancer at the apex of the lung, aneurysm in the aorta or its early branches, or enlargement of cervical glands. With involvement of the third neuron, anhidrosis may be absent, for fibers for sweating leave those for miosis and ptosis at the bifurcation of the common carotid and follow the external carotid artery. Aneurysm of the internal carotid artery is the most frequent cause of interruption of the third neuron.

Jaffe's [25] contribution is thorough and compact and altogether admirable.

The location of the pupillary fibers within the optic nerve, at least in its intracanalicular portion, is identified by François and Deweer [26] as at the nasal periphery of the optic nerve. In support of their contention, they present two of their own cases and 15 gathered from the literature in which loss of vision was exhibited in the temporal field in addition to loss of the pupillary reflex to light. This places the site of damage in the nasal part of the nerve.

In a neat, concise summary, and report of a single case, Kern [27] calls to the attention of general practitioners the resemblance of Adie's syndrome to tabes dorsalis. His patient, a woman aged 27, had been referred to him for treatment for

25. Jaffe, N. S.: Localization of Lesions Causing Horner's Syndrome, Arch. Ophth. **44**:710-728 (Nov.) 1950.

26. François, J., and Deweer, J. P.: Dissociation entre la fonction visuelle et la fonction pupillo-motrice du nerf optique, Ann. d'ocul. **183**:913-927 (Nov.) 1950.

27. Kern, A. B.: Adie's Syndrome: A Benign Disorder Simulating Tabes Dorsalis, J. A. M. A. **145**:230-231 (Jan. 27) 1951.

syphilis, when she had only a myotonic pupil and absence of tendon reflexes (Adie's syndrome). These findings, first noted during the course of a premarital examination, had been interpreted by the original physician as signs of syphilis and led to unnecessary embarrassment.

Gaines [28] reports two cases of postdiphtheritic cycloplegia, in girls of 11 and 9 years, with uneventful recovery in both. In one case the cycloplegia persisted for 10 weeks, and in the other for seven weeks; during that period bifocal lenses were worn, with satisfaction. One girl lost her voice and was unable to speak above a whisper for 12 days; the second suffered from transient palatal paralysis. In both cases pupillary reactions were retained throughout the disability. This is usual in diphtheria, but remarkable nonetheless.

OCULAR MOVEMENTS

Bilateral internuclear ophthalmoplegia (paralysis of both medial rectus muscles on attempted conjugate lateral gaze) is almost invariably due to multiple sclerosis, and consequently is a fairly reliable diagnostic sign of this disease. When the internuclear paralysis is unilateral, it may be due to multiple sclerosis; but, as shown by Cogan and associates,[29] it is more likely to be the result of infarction from vascular disease. The lesion involves the medial longitudinal fasciculus at the pons in the floor of the fourth ventricle near the midline. Cogan and associates report eight cases, and in one case necropsy findings are included. In that case, a small area of infarction involved the left medial longitudinal fasciculus, and the left medial rectus muscle had been paralyzed. In six of the cases nystagmus was present, and in an equal number, skew deviation. The higher eye was on the side of the paretic medial rectus muscle in all but one of these six cases.

To the almost innumerable causes of isolated abducens paralysis, Yaskin and Boles [30] add another possibility in their report of two cases of brucellosis in men.

The only known case of unilateral total ophthalmoplegia to follow spinal anesthesia is reported by Shapira, Schall, and Rodin.[31] Recovery occurred except in the lateral rectus muscle. The superior orbital fissure is postulated as being the site of the lesion causing the paralysis.

Nasal sinusitis was the cause of ocular paralysis in 10 cases presented by Dimsdale and Phillips.[32] In four cases, in which there was chronic sphenoiditis, the symptoms were double vision and headache, without fever or nasal symptoms. Diagnosis was made from the roentgenogram. Partial or complete recovery followed surgical drainage of the infected sphenoid sinus. In the six other cases inflammation of the superior orbital fissure caused double vision, unilateral headache, and a varying degree of nasal symptoms, unilateral papilledema, and trigeminal

28. Gaines, T. R.: Postdiphtheritic Cycloplegia: Report of 2 Cases, Arch. Ophth. **45**:416-418 (April) 1951.

29. Cogan, D. G.; Kubik, C. S., and Smith, W. L.: Unilateral Internuclear Ophthalmoplegia: Report of Eight Clinical Cases with One Postmortem Study, Arch. Ophth. **44**:783-796 (Dec.) 1950.

30. Yaskin, J. C., and Boles, R. S.: Abducens Paralysis in Brucellosis: Report of Two Cases, Am. J. Ophth. **33**:1277-1280 (Aug.) 1950.

31. Shapira, T. M.; Schall, S. and Rodin, M.: Total Unilateral Ophthalmoplegia Following Spinal Anesthesia, Am. J. Ophth. **33**:970-972 (June) 1950.

32. Dimsdale, H., and Phillips, D. G.: Ocular Palsies with Nasal Sinusitis, J. Neurol., Neurosurg. & Psychiat. **13**:225-236 (Aug.) 1950.

involvement. All showed roentgenologic evidence of disease of one or more of the nasal sinuses. Satisfactory recovery was achieved, in part through natural resistance of the tissues.

Periodic alternating nystagmus is reported by Gorman and Brock [33] in a case of Friedreich's ataxia. On forward gaze, there was spontaneous nystagmus to one side for one minute, then 10 seconds without nystagmus, and then nystagmus to the opposite side for one minute. These cycles continued regularly for several months. Dimsdale and Phillips were unable to advance a satisfactory explanation.

Miners' nystagmus remains a perplexing problem in spite of all that has been written about it over many years. Two more articles published during the past year fail to clarify the situation. Stern [34] speculates in a theoretical fashion on the psychologic basis of miners' nystagmus, maintaining that the precipitating cause of the breakdown in miners' nystagmus is oftenest a feeling of inability to cope with the work; the next most frequent cause is anxiety connected with the danger of occupation.

A sensible refutation by Browne, Beck, and Saint [35] appeared a few months later in the form of an occupational and social study. Observing adequate controls, they conclude that persons with miners' nystagmus are no more neurotic than others, and that the nature of their symptoms warrants the anxiety displayed, and the subsequent unemployment and financial hardship, the depression.

Two comprehensive reviews of the general aspects of nystagmus appeared during the past year, one by Spaeth [36] and another by Gorman and Brock.[37] The reader unfamiliar with the literature in this field may find them somewhat frustrating, although the authors, in the space at their disposal, have presented surveys that are as clear as one can expect in the present state of knowledge of nystagmus.

Two other articles that cannot be abstracted here deserve mention. Lyle [38] presents data on the ocular palsies associated with general diseases in a manner that should appeal especially to beginners in the study of ophthalmology. Writing for the experienced ophthalmologist, Krewson [39] discusses the diagnosis of paralysis of multiple ocular muscles, stressing various diagnostic methods and giving thoughtful evaluation to confusing factors.

MISCELLANEOUS CONDITIONS

In a statistical study of 358 cases of brain tumor, Petrohelos and Henderson [40] evaluate the ocular signs in diagnosis. Papilledema occurred in 60% of their cases

33. Gorman, W. F., and Brock, S.: Periodic Alternation Nystagmus in Friedreich's Ataxia, Am. J. Ophth. **33**:860-864 (June) 1950.

34. Stern, E. S.: The Psychiatric Aspect of Miners' Nystagmus, Brit. J. Ophth. **34**:385-390 (June) 1950.

35. Browne, R. C.; Beck, I. F., and Saint, E. G.: A Comparative Study of Coal Miners' Nystagmus, Brit. J. Ophth. **34**:601-620 (Oct.) 1950.

36. Spaeth, E. B.: Nystagmus: Its Diagnostic Significance, Arch. Ophth. **44**:549-560 (Oct.) 1950.

37. Gorman, W. F., and Brock, S.: Nystagmus: Its Mechanism and Significance, Am. J. M. Sc. **220**:225-233 (Aug.) 1950.

38. Lyle, T. K.: Ocular Palsies Associated with General Diseases, Australian & New Zealand J. Surg. **20**:43-51 (Aug.) 1950.

39. Krewson, W. E., III.: Diagnosis of Multiple Ocular Muscle Paralyses, J. A. M. A. **144**:534-537 (Oct. 14) 1950.

40. Petrohelos, M. A., and Henderson, J. W.: The Ocular Findings of Intracranial Tumor: A Study of 358 Cases, Tr. Am. Acad. Ophth. **55**:89-98 (Nov.-Dec.) 1950.

and nystagmus in 11%. Neither anisocoria nor paralysis of extraocular muscles is of much value in lateralization. Changes in the visual fields were present in nearly half the cases in which visual fields were examined, but no comment was made regarding their diagnostic reliability.

Papilledema may be due to a local inflammatory condition, to exogenous toxins, to local metabolic disturbance, or to congestion secondary to increased intracranial pressure. Leinfelder [41] is not satisfied that the appearance of choked disk is explained by the prevalent concept of pressure on the central retinal vein as it passes through the subarachnoid space. He states that the capillaries of the nerve head are derived from the choroidal circulation through the arterial circle of Zinn. Venous drainage is by way of the central retinal vein. Two other exits are possible but have not been demonstrated: (1) that into the choroidal circulation and out by short posterior ciliary veins, and (2) that into the subdural space, where there are veins in the inner sheath of the optic nerve.

In writing on the differential diagnosis of papilledema and optic neuritis, Davies [42] provides an excellent description of the ophthalmoscopic appearance of each. He points out, in papillitis, the rapid loss of vision, the pain on movement of the eyeball, the tenderness to pressure on the globe, and the lack of sustained contraction of the pupil to light stimulus, and, in papilledema, the transient episodes of blurred vision and headache from increased intracranial pressure. His lists of possible causes of papilledema and of optic neuritis are so all-inclusive, however, that the reader may be perplexed, for there is no indication of what is important and what is rare or dubious. Lists based on his own personal experience would have been more convincing and would have maintained the high level of the rest of the paper.

Donahue,[43] continuing his interest in problems related to migraine, reviews four types of headaches that are not migraine. Histamine headache is excruciating, sudden in onset, and associated with profuse tearing and congestion of the eye, stuffiness of the nose, and increased surface temperature, all on the side of the pain. Ischemia of muscles, with vasoconstriction as a factor, causes localized painful areas in the muscles of the head and neck. Hypoglycemia causes unilateral headache, preceded by a period of weakness, drowsiness, and nervousness. Headache attributable to aneurysm is associated with involvement of the oculomotor and trigeminal nerves.

The origin of ocular paralysis occurring in the course of migraine remains unexplained. Of several concepts offered to explain it, that of cerebral aneurysm has received wide acceptance, although there has been little evidence to support it. Alpers and Yaskin [44] tested the validity of this concept on two patients with

41. Leinfelder, P. J.: Choked Disk and Other Types of Edema of the Nerve Head: Comment on the Physiopathologic Features, J. A. M. A. **144**:919-920 (Nov. 11) 1950.

42. Davies, R. H.: Differential Diagnosis Between Papilledema and Optic Neuritis, Kresge, Eye Inst. Bull. **1**:44-53 (Feb.) 1950.

43. Donahue, H. C.: Migrainoid Headaches: Their Ocular Manifestations, Arch. Ophth. **44**:285-292 (Aug.) 1950.

44. Alpers, B. J., and Yaskin, H. E.: Pathogenesis of Ophthalmoplegic Migraine, A. M. A. Arch. Ophth. **45**:555-566 (May) 1951.

ophthalmoplegic migraine by arteriographic study. In one of them the procedure caused thrombosis in the middle cerebral artery and death two days later. Neither patient had an aneurysm. From the clinical evidence at hand, the authors deem it advisable to regard ophthalmoplegic migraine as a true entity. Incidentally, they offer a splendid summary of the published literature on the subject.

In a thesis written for the American Ophthalmological Society, Burch [45] discusses at length the psychoneurotic reaction patterns in ophthalmology. He covers so many aspects that it is not feasible to abstract his paper here.

45. Burch, E. P.: Psychoneurotic Reaction Patterns in Ophthalmology, Tr. Am. Ophth. Soc. 48:370-394, 1950.

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Postgraduate Clinical Session, Virginia Society of Ophthalmology and Otolaryngology.—The Postgraduate Clinical Session sponsored by the Virginia Society of Ophthalmology and Otolaryngology will be held in Baruch Auditorium, Richmond, on Nov. 27 to 30, 1951. The first two days will be devoted to otolaryngology, and the remaining two days to ophthalmology. For further information, write Dr. Peter N. Pastore, chairman, Box 25, Medical College of Virginia Station, 1200 E. Broad St., Richmond, Va.

CORRECTION

In the paper entitled "Cortisone Therapy in Case of Rheumatoid Nodules of the Eye in Chronic Rheumatoid Arthritis," by William L. Mundy, M.D.; Royal M. Howard, M.D.; Paul H. Stillman, M.D., and Margaret Bevans, M.D., published in the May 1951 issue of the ARCHIVES, page 531 the authors wish to clarify the following points:

1. In legends for Figures 1 and 3 "sclera" should read "episclera."

2. The following reference should be added: Verhoeff, F. H., and King, M. J.: Scleromalacia Perforans, ARCH. OPHTH. 20:1013-1035 (Dec.) 1938.

Book Reviews

The Neuroses: Diagnosis and Management of Functional Disorders and Minor Psychoses. By Walter C. Alvarez, M.D. Price, $10. Pp. 667. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia, 1951.

The author states that he has written this book for the young physician who desires instruction in the diagnosis and treatment of functional troubles. It would be difficult to imagine any practicing physician who would not find much of value in this interesting, instructive, and easily readable book.

Specifically, Dr. Alvarez gives many hints and practical suggestions for the diagnosis of the neuroses and psychoses. The causes of nervous imbalance and neuroses are discussed. Personality types and their related syndromes are explained. The chapters on treatment display a philosophy in medicine which is frequently overlooked in teaching in this busy day of laboratory tests and roentgenograms.

There is only a small portion of the book devoted to psychosomatic symptoms seen by the ophthalmologist, but it would be a mistake to feel that the value to the ophthalmologist stops here. Any doctor who treats patients will find specific items of interest on almost every page, whether it is hints on sizing up the patient from the point of view of clothes, mannerisms, and speech, or suggestions for the successful physician who finds his practice too large and must somehow make adjustments if he is to see all those who want to see him, at reasonable fees, and still have time to give adequate examination and treatment.

Chronology of Ophthalmic Development. By Arthur H. Keeney, M.D. Price, $2. Pp. 32. Charles C Thomas, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

This is a valuable and comprehensive collection of data on the development of the human eye. Because of its conciseness, it makes an easy reference from which to obtain precise data. It is not intended to replace texts on the development of the human eye, but is meant to be used in conjunction with these. The author has made a unique and helpful contribution to ophthalmic literature.

CORRECTION

In the Annual Review on "Strabismus" by Dr. Hermann M. Burian, published in the July issue of the ARCHIVES, page 89, the fourth sentence of the fifth paragraph should read: "Under these circumstances, one could hardly expect a normal adduction of the eyes, and one wonders whether this might not be due to mechanical factors rather than to a disturbance in the median longitudinal faciculus."

In the review of the 22d edition of *Dorland's* "American Illustrated Medical Dictionary" published in the July issue of the ARCHIVES, page 112, it was incorrectly stated that there is no reference to retrolental fibroplasia and the collagen diseases in the dictionary. Retrolental fibroplasia is defined as a subentry under "fibroplasia," and the collagen diseases are covered as subentries under "diseases."

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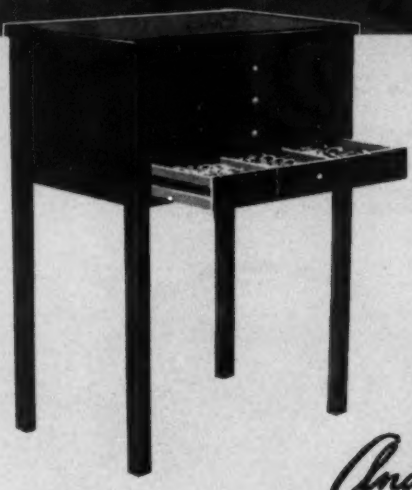

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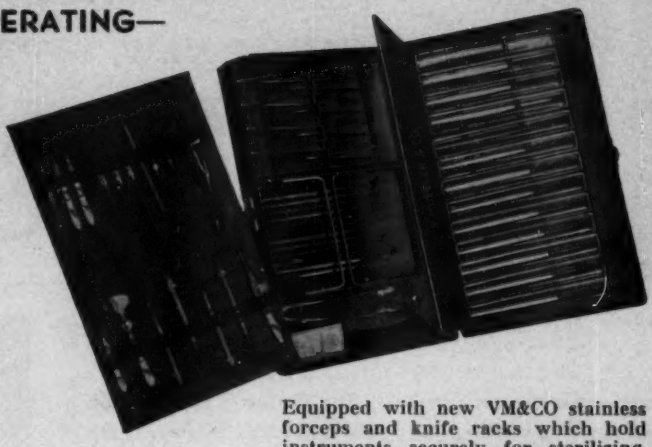

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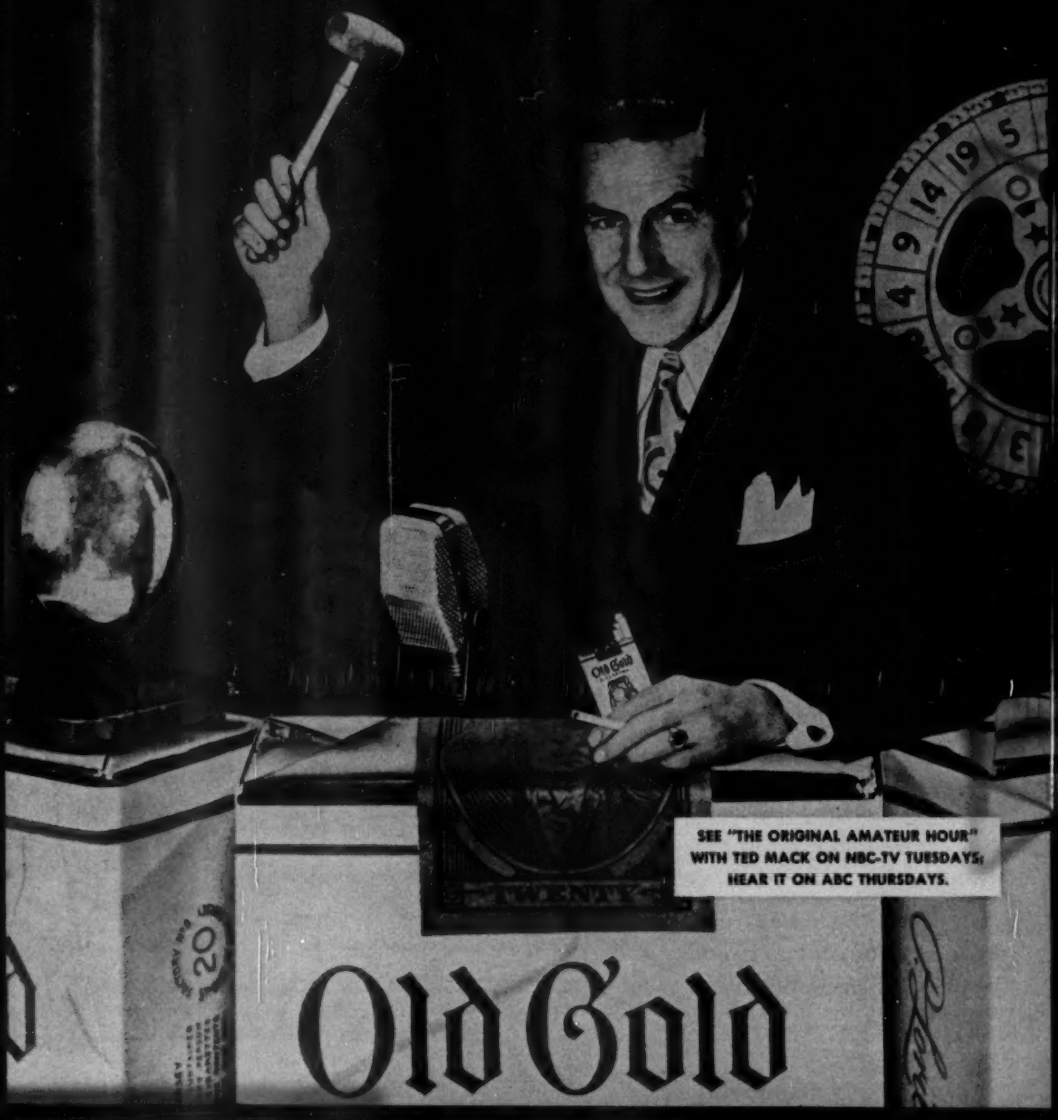

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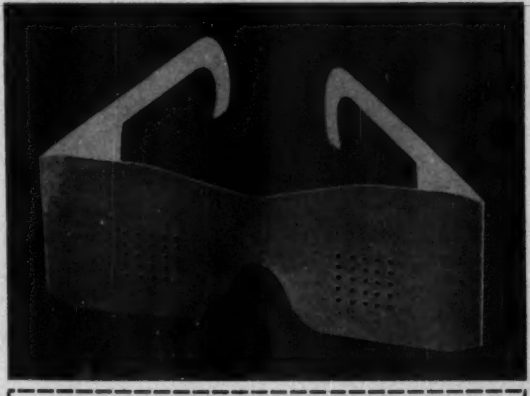

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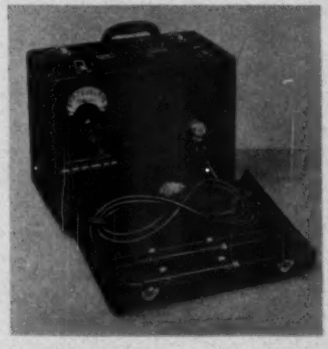

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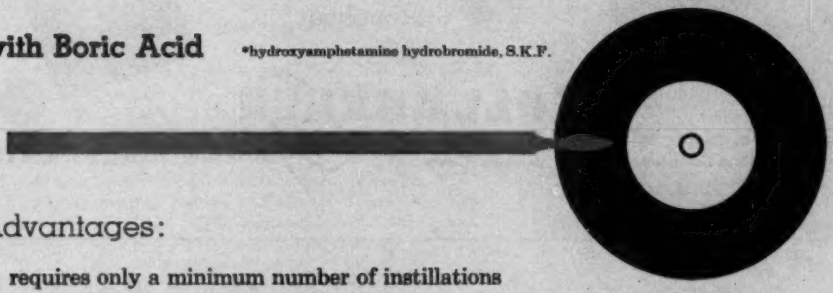

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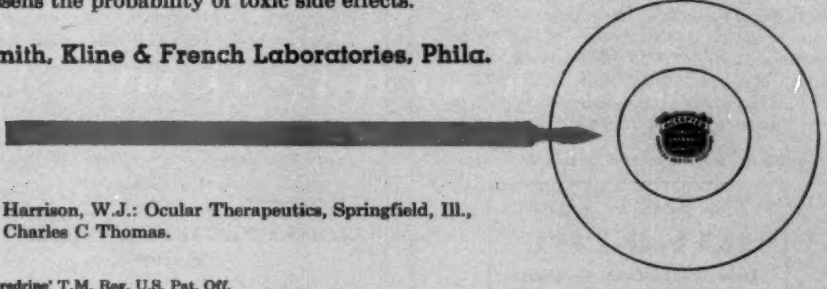

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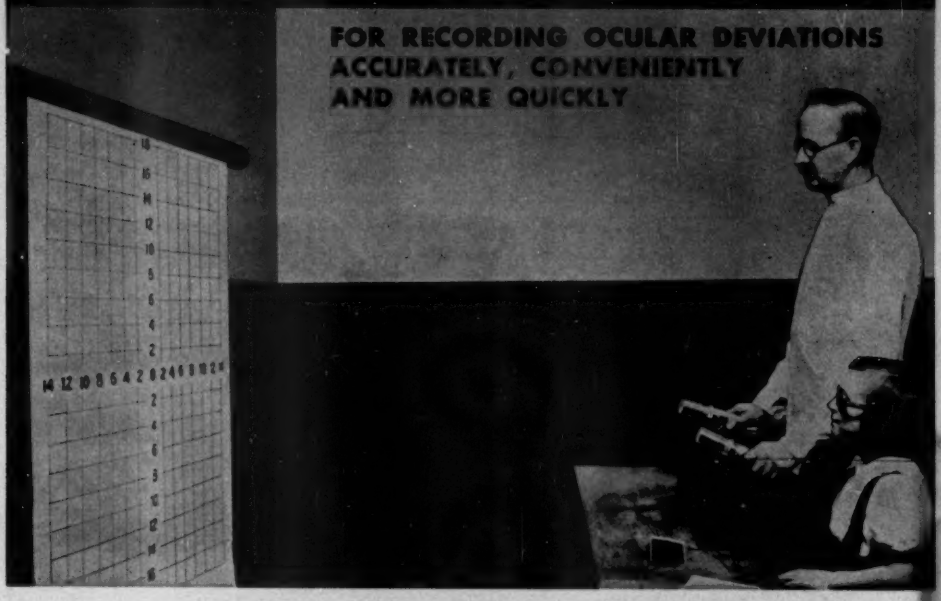

Use of the Lancaster Red-Green Test greatly facilitates the process of examining cases of disturbance of ocular motility. While it is not claimed to be superior to all other tests in all cases and conditions, its advantages are so many and so obvious as to make it highly useful to the modern practitioner. With the Lancaster Red-Green Test, for example:

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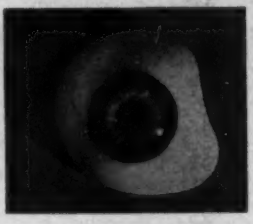

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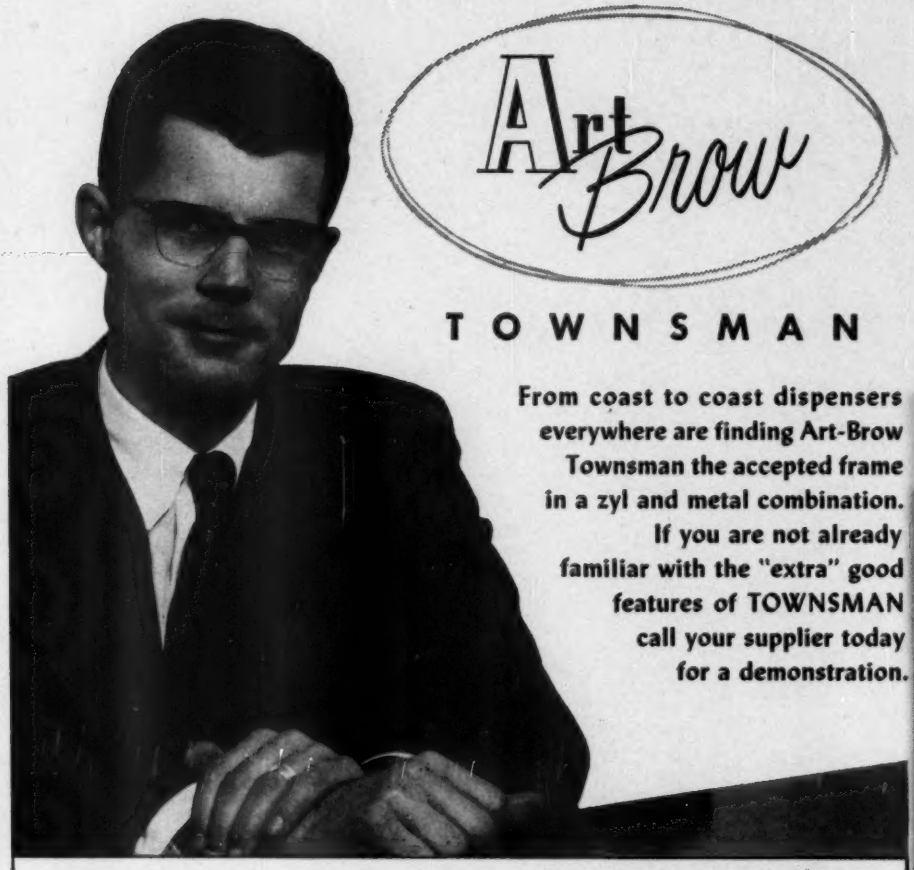

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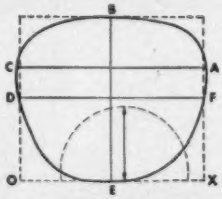

EYE	AC x BE	DF x BE	BRIDGE
42	44 x 38	42 x 38	20-22-24
44	46 x 40	44 x 40	20-22-24-26
46	48 x 42	46 x 42	20-22-24-26
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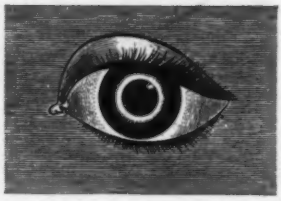

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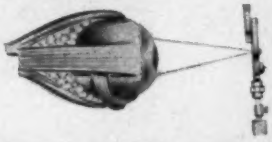
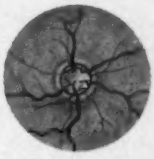
1/8% solution.
For rapid relief of congestion, itching, smarting and lacrimation.



REFRACTION, FUNDUSCOPIC EXAMINATION:
2.5% solution or 1% emulsion.
For prompt and short acting mydriasis virtually free from cycloplegia.

UVEITIS, POSTERIOR SYNECHIAE:
10% solution or 10% emulsion.
For freeing recently formed posterior synechiae as well as for prevention of synechiae formation in uveitis (with atropine).



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10% solution, 10% emulsion or 2.5% solution.
For temporary reduction of intra-ocular tension and for the provocative test for angle block.

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